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(54) Antirhinoviral piperidinyl, pyrrolidinyl and piperazinyl alkylphenol ethers.

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CHEMICAL ABSTRACTS, vol. 88, no. 25, June
19, 1978, Columbus, Ohio, USA; ANGIER R.B.
et al.: "Antirhinovirus agents", page 766, col-
umn 2, abstract-no. 190 813e

(56) References cited :
CHEMICAL ABSTRACTS, vol. 101, no. 21,
November 19, 1984, Columbus, Ohio, USA;
POLIVKA Z. et al.: "Potential hypnotics and
anxiolytics: synthesis of 2-bromo-4-(2-
chlorophenyl)-9-[4-(2-methoxyethyl)piperazi-
no]-6H-thieno[3,2-f]-1,2,4-triazolo[4,3-a]-1,4-
diazepine and of some related compounds",
page 765, column 1, abstract-no. 191 861t

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EP 0 398 425 B1

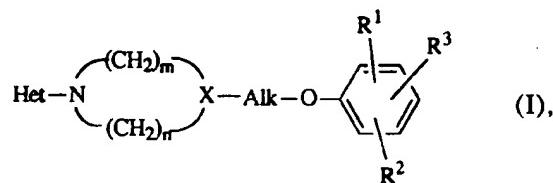
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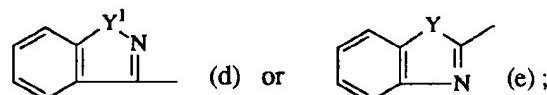
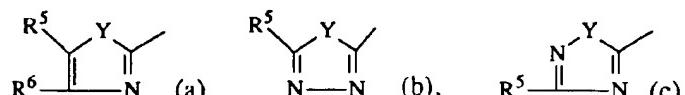
In EP-A-0,156,433 there are described antivirally active pyridazinamines. Further antiviral agents are described in US-4,451,476; in EP-A-0,137,242 and in EP-A-0,207,453. DE-A-3,530,089, published March 6, 1986 discloses 3-[4-(2-phenoxyethyl)-1-piperazinyl]-1,2-benzisothiazole and 3-[4-(4-phenoxybutyl)-1-piperazinyl]-1,2-benzisothiazole as analgesics.

The compounds of the present invention differ from the cited art compounds by the fact that they are substituted with an oxazol, thiazol, thia(dia)zol, oxa(dia)zol, benz(is)othiazol and benz(is)oxazol moiety in a previously undisclosed manner and particularly by their favourable antirhinoviral properties.

The present invention is concerned with novel piperidinyl, pyrrolidinyl and piperazinyl alkylphenol ethers of formula :



20 the addition salts thereof and the stereochemically isomeric forms thereof, wherein
Het represents a heterocycle of formula:



35 Y is O or S; Y1 is O, S or SO₂; and
R⁵ and R⁶ each independently are hydrogen, trifluoromethyl, halo, amino,
C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkyloxycarbonyl or aryl; and

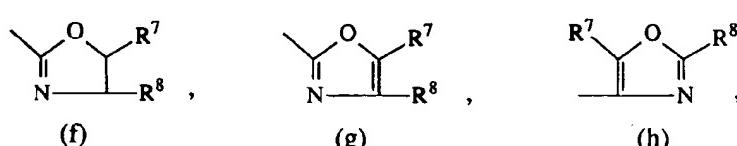
40 m and n each independently are integers of from 1 to 4 inclusive, with the sum of m and n being 3, 4 or 5;

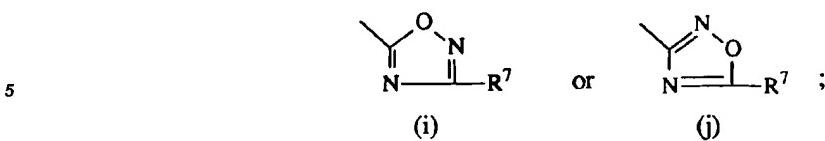
X is N or CH;

Alk is C₁₋₄alkanediyl;

R¹ and R² each independently are hydrogen, C₁₋₄alkyl or halo;

45 R³ is hydrogen, halo, cyano, C₁₋₄alkyloxy, aryl or -COOR⁴, with R⁴ being hydrogen, C₁₋₄alkyl, arylC₁₋₄alkyl, C₃₋₆cycloalkylC₁₋₄alkyl, C₃₋₅salkenyl, C₃₋₅salkynyl or C₁₋₄alkyloxyC₁₋₄alkyl; or R³ is a radical of formula





¹⁰ R⁷ and R⁸ each independently are hydrogen, C₁₋₄alkyl, aryl or arylC₁₋₄alkyl;
wherein each aryl is phenyl being optionally substituted with 1 or 2 substituents each independently selected from halo, C₁₋₄alkyl, trifluoromethyl, C₁₋₄alkyloxy or hydroxy, provided that Y¹ is other than S when R¹, R² and R³ represent hydrogen, X is N and m and n are both 2.

As used in the foregoing definitions the term "halo" is generic to fluoro, chloro, bromo and iodo; the term "C₁₋₄alkyl" defines straight and branch chained saturated hydrocarbon radicals, having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, 1-methylethyl, butyl, 1,1-dimethylethyl and the like; the term "C₃₋₆cycloalkyl" is generic to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; the term "C₃₋₅alkenyl" defines straight and branch chained hydrocarbon radicals containing one double bond and having from 3 to 5 carbon atoms such as, for example, 2-propenyl, 3-but enyl, 2-but enyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-but enyl and the like; "C₃₋₅alkynyl" defines straight and branch chained hydrocarbon radicals containing one triple bond and having from 3 to 5 carbon atoms such as, propargyl, 2-butynyl, 3-butynyl, 2-pentynyl, 3-pentynyl or 4-pentynyl, and when a C₃₋₅alkenyl or C₃₋₅alkynyl is substituted on a heteroatom, then the carbon atom of said C₃₋₅alkenyl or C₃₋₅alkynyl connected to said heteroatom preferably is saturated. "C₁₋₄alkanediyl" defines a bivalent straight or branch chained hydrocarbon radical having from 1 to 4 carbon atoms.

The said addition salts as mentioned hereinabove are meant to comprise the therapeutically active, and in particular, pharmaceutically acceptable, non-toxic addition salt forms which the compounds of formula (I) are able to form. The acid addition salts can conveniently be obtained by treating the base form with appropriate acids such as, for example, inorganic acids, such as hydrohalic acid, e.g. hydrochloric, hydrobromic and the like, and sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids such as, for example, acetic, hydroxyacetic, propanoic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexane-sulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form. The compounds of formula (I) containing acidic protons may also be converted into their therapeutically active, and in particular, pharmaceutically acceptable, non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. The term addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

From formula (I) it is evident that the compounds of this invention may have asymmetric carbon atoms in their structure. The absolute configuration of this centre may be indicated by the stereochemical descriptors R and S, this R and S notation corresponding to the rules described in Pure Appl. Chem. 1976, 45, 11-30. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure. Stereochemically isomeric forms of the compounds of formula (I) are intended to be embraced within the scope of the invention.

Particular compounds of formula (I) are those compounds within the invention wherein Het is a radical of formula (a) wherein R⁵ is hydrogen or halo and R⁶ is hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl or aryl, or a radical of formula (b) wherein R⁵ is hydrogen, C₁₋₄alkyl, halo, amino or aryl, or a radical of formula (c) wherein R⁵ is hydrogen, C₁₋₄alkyl or aryl, or a radical of formula (d) or (e) and/or n is 1.2, or 3.

Other particular compounds are those compounds within the invention wherein R¹ and R² each independently are hydrogen or halo; and/or R³ is a radical of formula -COOR⁴ wherein R⁴ represents C₁₋₄alkyl, C₃₋₅alkenyl, C₃₋₆alkynyl or C₁₋₄alkyloxyC₁₋₄alkyl, or R³ is a heterocycle of formula (f), (g), (h), (i) or (j) wherein R⁷ and R⁸ each independently represent hydrogen or C₁₋₄alkyl, said R³ being preferably located on the 4-position.

Among the above subgroups those compounds of formula (I) are preferred wherein Het is a radical of formula (a) wherein R⁵ is hydrogen and R⁶ is hydrogen or C₁₋₆alkyloxycarbonyl; or a radical of formula (b) wherein

R^5 is hydrogen, C_{1-4} alkyl, halo or aryl; or a radical of formula (d) where Y^1 is SO_2 ; or a radical of formula (e); and/or R^1 and R^2 are both hydrogen; and/or R^3 is C_{1-4} alkyloxycarbonyl or a 1,2,4-oxadiazol-5-yl of formula (i) wherein R^7 represents C_{1-4} alkyl.

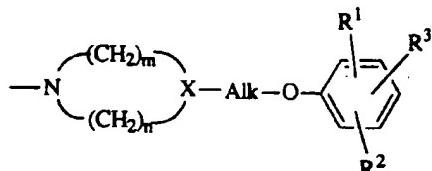
5 More preferred compounds of formula (I) are those preferred compounds wherein n and m are both 2 and Het is a radical of formula (b) wherein R^5 represents hydrogen, methyl, ethyl, chloro, bromo or iodo, and Y is S.

10 Particularly preferred compounds within the invention are those more preferred compounds wherein Het is a radical of formula (b) wherein R^5 is methyl or bromo and R^3 is methoxycarbonyl, ethoxycarbonyl or 3-ethyl-1,2,4-oxadiazol-5-yl.

The most preferred compounds of the invention are selected from ethyl 4-[2-[1-(5-methyl-1,3,4-thiadiazol-2-yl)-4-piperidinyl]ethoxy]benzoate, ethyl 4-[2-[1-(5-bromo-1,3,4-thiadiazol-2-yl)-4-piperidinyl]ethoxy]benzoate, 1-(5-bromo-1,3,4-thiadiazol-2-yl)-4-[2-[4-(3-ethyl-1,2,4-oxadiazol-5-yl)phenoxy]ethyl]piperidine, and the pharmaceutically acceptable acid addition salts thereof.

15 In order to simplify the structural representations of the compounds of formula (I) and of certain materials and intermediates thereof, the radical

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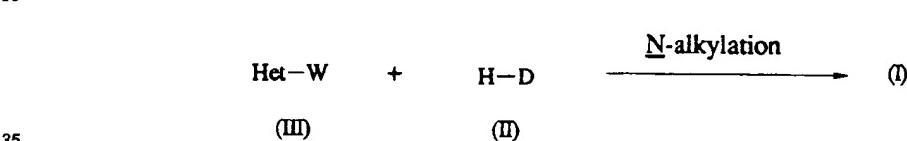


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will hereafter be represented by the symbol D.

The compounds of formula (I) can generally be prepared by reacting an amine of formula (II) with a heterocycle of formula (III) following art-known N-alkylation procedures.

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In the foregoing and following reaction schemes W represents an appropriate reactive leaving group such as, for example, halo, e.g. fluoro, chloro, bromo, iodo, or in some instances W may also be a sulfonyloxy group, e.g. 4-methylbenzenesulfonyloxy, benzenesulfonyloxy, 2-naphthalenesulfonyloxy, methanesulfonyloxy, trifluoromethanesulfonyloxy and the like reactive leaving groups.

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The N-alkylation reaction can conveniently be carried out by mixing the reactants, optionally in a reaction-inert solvent such as, for example, water; an aromatic solvent, e.g. benzene, methylbenzene, dimethylbenzene, chlorobenzene, methoxybenzene and the like; a C_{1-8} alkanol, e.g. methanol, ethanol, 1-butanol and the like; a ketone, e.g. 2-propanone, 2-butanone, 4-methyl-2-pentanone and the like; an ester, e.g. ethyl acetate, γ -butyrolactone and the like; an ether, e.g. 1,1'-oxybisethane, tetrahydrofuran, 1,4-dioxane and the like; a dipolar aprotic solvent, e.g. N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, pyridine, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, 1,3-dimethyl-2-imidazolidinone, 1,1,3,3-tetramethylurea, 1-methyl-2-pyrrolidinone, nitrobenzene, acetonitrile and the like; or a mixture of such solvents. The addition of an appropriate base such as, for example, an alkali metal or an earth alkaline metal carbonate, hydrogen carbonate, hydroxide, oxide, carboxylate, alkoxide, hydride or amide, e.g. sodium carbonate, sodium hydrogen carbonate, potassium carbonate, sodium hydroxide, calcium oxide, sodium acetate, sodium methoxide, sodium hydride, sodium amide and the like, or an organic base such as, for example, a tertiary amine, e.g. N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, 4-ethylmorpholine, 1,4-diazabicyclo[2.2.2]octane, pyridine and the like, may optionally be used to pick up the acid which is formed during the course of the reaction.

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In some instances the addition of a iodide salt, preferably an alkali metal iodide, e.g. potassium iodide or a crown ether, e.g. 1,4,7,10,13,16-hexaoxacyclooctadecane and the like, may be appropriate. Stirring and somewhat elevated temperatures may enhance the rate of the reaction; more in particular the reaction may be conducted at the reflux temperature of the reaction mixture. Additionally, it may be advantageous to conduct said

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55 In some instances the addition of a iodide salt, preferably an alkali metal iodide, e.g. potassium iodide or a crown ether, e.g. 1,4,7,10,13,16-hexaoxacyclooctadecane and the like, may be appropriate. Stirring and somewhat elevated temperatures may enhance the rate of the reaction; more in particular the reaction may be conducted at the reflux temperature of the reaction mixture. Additionally, it may be advantageous to conduct said

N-alkylation reaction under an inert atmosphere such as, for example, oxygen-free argon or nitrogen gas.

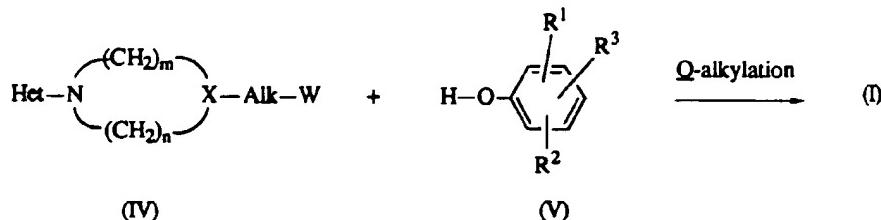
Alternatively, said N-alkylation reaction may be carried out by applying art-known conditions of phase transfer catalysis reactions. Said conditions comprise stirring the reactants, with an appropriate base and optionally under an inert atmosphere as defined hereinabove in the presence of a suitable phase transfer catalyst such as, for example, a trialkylphenylmethylammonium, tetraalkylammonium, tetraalkylphosphonium, tetraarylpophosphonium halide, hydroxide, hydrogen sulfate and the like catalysts. Somewhat elevated temperatures may be appropriate to enhance the rate of the reaction.

In this and the following preparations, the reaction products may be isolated from the reaction mixture and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, distillation, crystallization, trituration and chromatography.

The compounds of formula (I) can also be prepared by alkylating a phenol of formula (V) with an intermediate of formula (IV).

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(IV)

(V)

(I)

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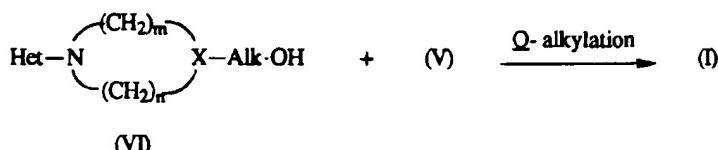
Said Q-alkylation reaction can conveniently be carried out by mixing the reactants, optionally in a reaction-inert solvent such as, for example, water; an aromatic solvent, e.g. benzene, methylbenzene, dimethylbenzene and the like; a C₁-₆alkanol, e.g. methanol, ethanol and the like; a ketone, e.g. 2-propanone, 4-methyl-2-pentanone and the like; an ester, e.g. ethyl acetate, γ-butyrolactone and the like; an ether, e.g. 1,1'-oxybisethane, tetrahydrofuran, 1,4-dioxane and the like; a dipolar aprotic solvent, e.g. N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide and the like; or a mixture of such solvents. The addition of an appropriate base such as, for example, an alkali metal or an earth alkaline metal carbonate, hydrogen carbonate, hydroxide, oxide, carboxylate, alkoxide, hydride or amide, e.g. sodium carbonate, sodium hydrogen carbonate, potassium carbonate, sodium hydroxide, calcium oxide, sodium acetate, sodium methoxide, sodium hydride, sodium amide and the like, or an organic base such as, for example, a tertiary amine, e.g. N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine and the like, may optionally be used to pick up the acid which is formed during the course of the reaction. Further, it may be advantageous to convert the intermediate of formula (V) first into a suitable salt form thereof such as, for example, an alkali or earth alkaline metal salt, by reacting (V) with an appropriate base as defined hereinabove and subsequently using said salt form in the reaction with the alkylating reagent of formula (IV). Stirring and somewhat elevated temperatures may enhance the rate of the reaction; more in particular the reaction may be conducted at the reflux temperature of the reaction mixture. Additionally, it may be advantageous to conduct said alkylation reaction under an inert atmosphere such as, for example, oxygen-free argon or nitrogen gas.

Alternatively, said Q-alkylation reaction may be carried out by applying art-known conditions of phase transfer catalysis reactions as described hereinbefore.

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The compounds of formula (I) can alternatively be prepared by reacting a phenol of formula (V) with an alcohol of formula (VI) in the presence of a mixture of diethyl azodicarboxylate and triphenylphosphine.

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(VI)

Q-alkylation

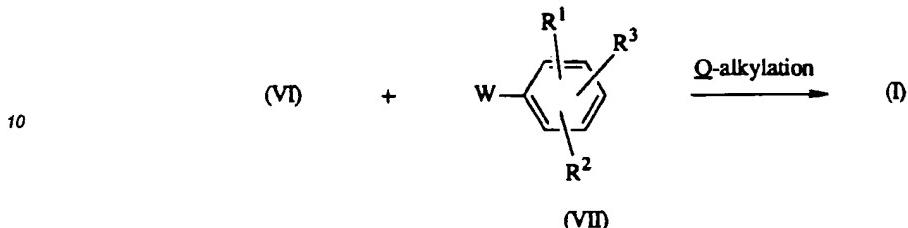
(I)

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The reaction of (VI) with (V) can conveniently be conducted in an anhydrous reaction-inert solvent preferably under mild neutral conditions at room temperature or below. A suitable reaction-inert solvent is, for example, an aliphatic hydrocarbon, e.g. hexane and the like, an ether, e.g. 1,1'-oxybisethane, 2,2'-oxybispropane, tetrahydrofuran, 1,4-dioxane and the like, a dipolar solvent, e.g. hexamethylphosphoric triamide, N,N-dimethylformamide and the like, or a mixture of such solvents.

The compounds of formula (I) may also be prepared by reacting an alcohol of formula (VI) with an appropriate reagent of formula (VII) according to the hereinbefore described O-alkylation procedures for the preparation of (I) from (IV) and (V).

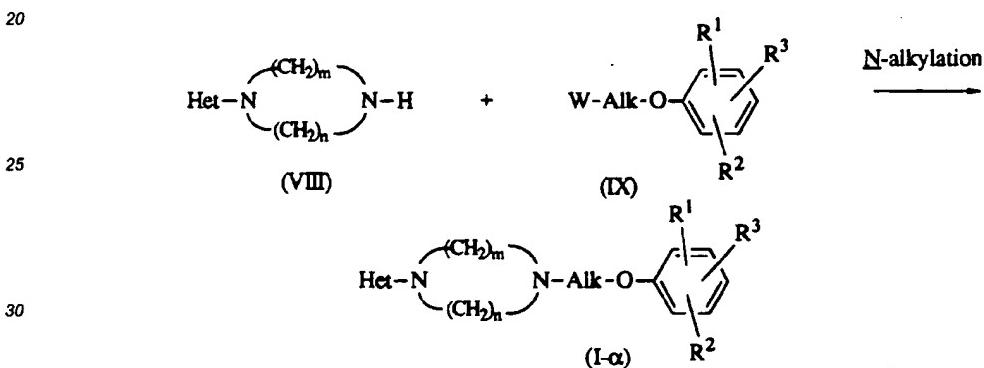
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The compounds of formula (I) wherein X is N said compounds being represented by (I- α), can also be prepared by N-alkylating a piperazine or an analogue thereof of formula (VIII) with a reagent of formula (IX) following similar procedures as described hereinbefore for the preparation of (I) starting from (II) and (III).

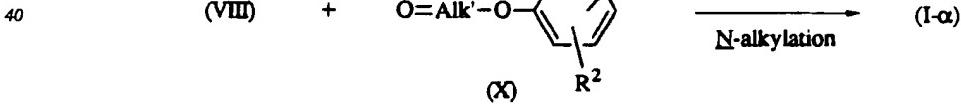
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The compounds of formula (I- α) can also be prepared by reductively N-alkylating an intermediate of formula (VIII) with a ketone or aldehyde of formula (X) following art-known reductive N-alkylation procedures.

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In formula (X) O=Alk'- represents a radical of formula H-Alk- wherein two geminal hydrogen atoms are replaced by oxygen.

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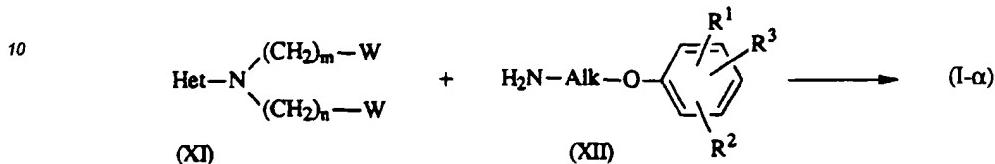
Said reductive N-alkylation reaction may conveniently be carried out by reducing a mixture of the reactants in a suitable reaction-inert solvent. In particular, the reaction mixture may be stirred and/or heated in order to enhance the reaction rate. Suitable solvents are, for example, water; C₁₋₆alkanols, e.g. methanol, ethanol, 2-

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propanol and the like; esters, e.g. ethyl acetate, γ -butyrolactone and the like; ethers, e.g. 1,4-dioxane, tetrahydrofuran, 1,1'-oxybisethane, 2-methoxyethanol and the like; halogenated hydrocarbons, e.g. dichloromethane, trichloromethane and the like; dipolar aprotic solvents, e.g. N,Ndimethylformamide, dimethylsulfoxide and the like; carboxylic acids, e.g. acetic acid, propanoic acid and the like; or a mixture of such solvents. The term "art-known reductive N-alkylation procedures" means that the reaction is carried out either with sodium cyanoborohydride, sodium borohydride, formic acid or a salt thereof, e.g. ammoniumformate, and the like reducing agents, or alternatively under a hydrogen atmosphere, optionally at an increased temperature and/or pressure, in the presence of an appropriate catalyst such as, for example, palladium-on-charcoal, platinum-on-charcoal and the like. In order to prevent the undesired further hydrogenation of certain functional groups in the reactants and the reaction products, it may be advantageous to add an appropriate catalyst-poison to

the reaction mixture, e.g., thiophene, quinoline-sulphur and the like. In some instances it may also be advantageous to add an alkali metal salt to the reaction mixture such as, for example, potassium fluoride, potassium acetate and the like salts.

- 5 Additionally the compounds of formula (I- α) may be prepared by cyclizing an intermediate of formula (XI) with an amine of formula (XII).



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The reaction is carried out by stirring the reactants in an appropriate organic solvent such as, for example, 2-propanol, cyclohexanol, 2-propanone and the like, optionally in admixture with an appropriate polar solvent preferably at an elevated temperature. Addition to the reaction mixture of an appropriate base, such as, for example, an alkali or an earth alkaline metal carbonate or hydrogen carbonate or an organic base such as, for example, a tertiary amine, e.g. N,N-diethylethanamine may be suited to pick up the acid which is liberated during the course of the reaction. In order to enhance the rate of the reaction a small amount of an appropriate iodide salt, e.g. sodium or potassium iodide may be added.

20 Compounds of formula (I) wherein X is CH, said compounds being represented by formula (I- β), may also be prepared by reacting a ketone (XIII) with an ylide of formula (XV) or by reacting an aldehyde (XIV) with an ylide of formula (XVI) in a reaction-inert solvent, following art-known Wittig reaction procedures (R^9 and R^{10} are aryl or C_{1-6} -alkyl) or Horner-Emmons reaction procedures (R^9 is alkoxy and R^{10} is O⁻). Appropriate solvents are, for example, hydrocarbons, e.g. hexane, heptane, cyclohexane and the like; ethers, e.g. 1,1'-oxybisethane, tetrahydrofuran, 1,2-dimethoxyethane and the like; dipolar aprotic solvents, e.g. dimethylsulfoxide, hexamethylphosphor triamide, and the like. Then the unsaturated intermediates (XVII) and (XVIII) can be reduced following an appropriate reduction procedure, for example, by stirring and, if desired, heating the unsaturated intermediates in a suitable reaction-inert solvent in the presence of hydrogen and an appropriate catalyst such as, for example, palladium-on-charcoal and the like catalysts. Suitable solvents are alkanols, e.g. methanol, ethanol and the like, and carboxylic acids, e.g. acetic acid and the like.

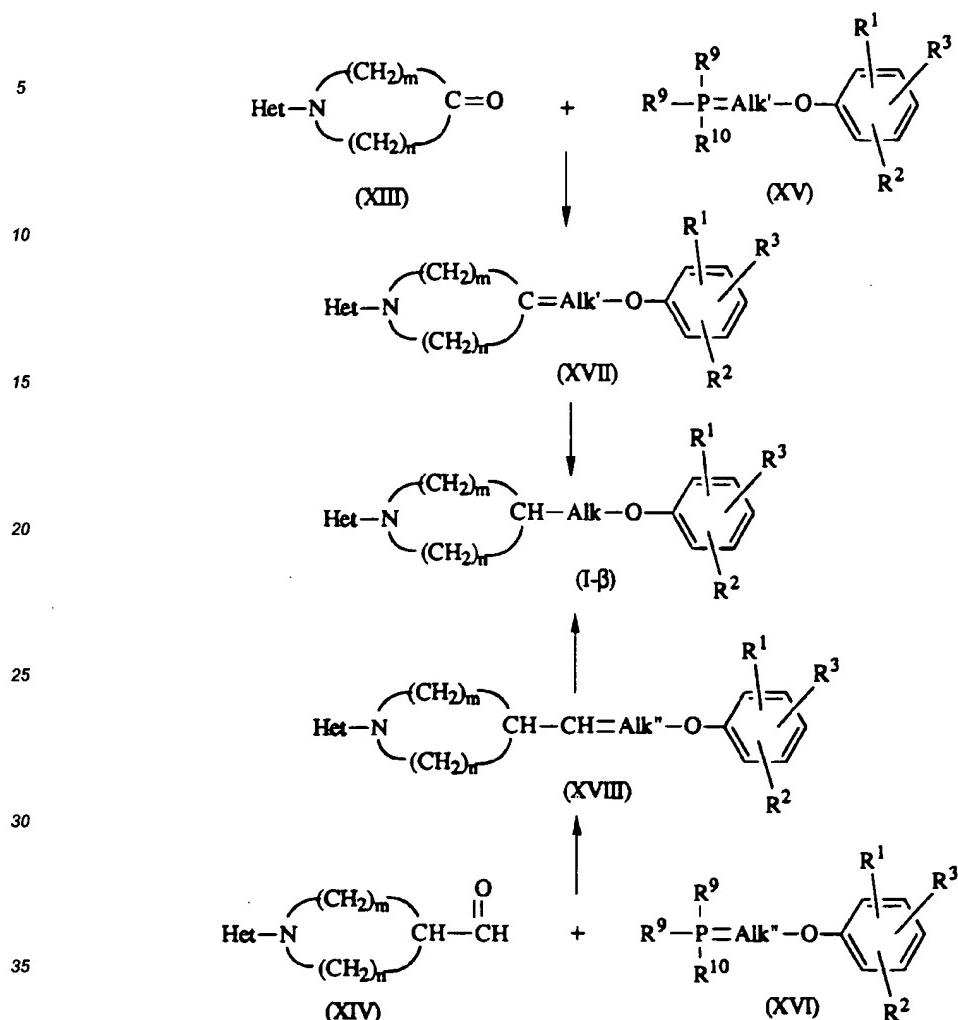
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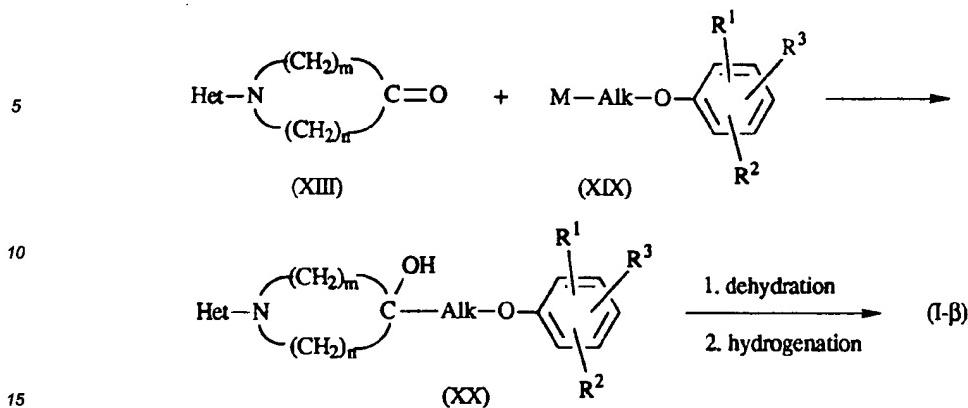
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The intermediate ylides of formulae (XV) and (XVI) can be obtained by treating a phosphonium salt or a phosphonate with an appropriate base such as, for example, potassium tert. butoxide, methylolithium, butyllithium, sodium amide, sodium hydride, sodium alkoxide and the like bases under an inert atmosphere and in a reaction-inert solvent such as, for example, an ether, e.g. tetrahydrofuran, 1,4-dioxane and the like. In (XV) (R⁹)₂R¹⁰P=Alk'- represents a radical of formula H-Alk- wherein two geminal hydrogen atoms are replaced by (R⁹)₂R¹⁰P=.

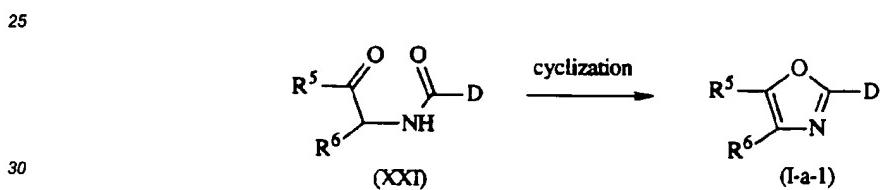
In (XVI) Alk" has the same meaning as Alk' with the proviso that one methylene is missing.

Alternatively, the compounds of formula (I-β) may be prepared by reacting a ketone (XIII) with an organometallic reagent of formula (XIX), wherein M represents a metal group such as, for example, lithium, halo magnesium, copper lithium and the like, in a reaction-inert solvent such as, for example, an ether, e.g. tetrahydrofuran, 1,1'-oxybisethane, 1,2-dimethoxyethane and the like. The thus prepared alkanol of formula (XX) may subsequently be dehydrated with an appropriate acid, e.g. hydrochloric or sulfuric acid, and hydrogenated to a compound of formula (I-β) following the procedure described hereinbefore for reducing an intermediate of formula (XVII) to a compound (I-β).

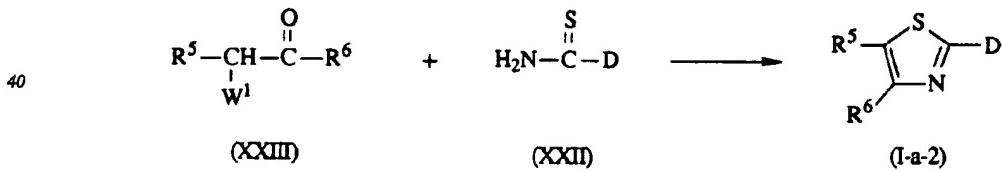


In a similar manner an aldehyde of formula (XIV) may also be reacted with an organometallic reagent, dehydrated and reduced to yield a compound of formula (I-β).

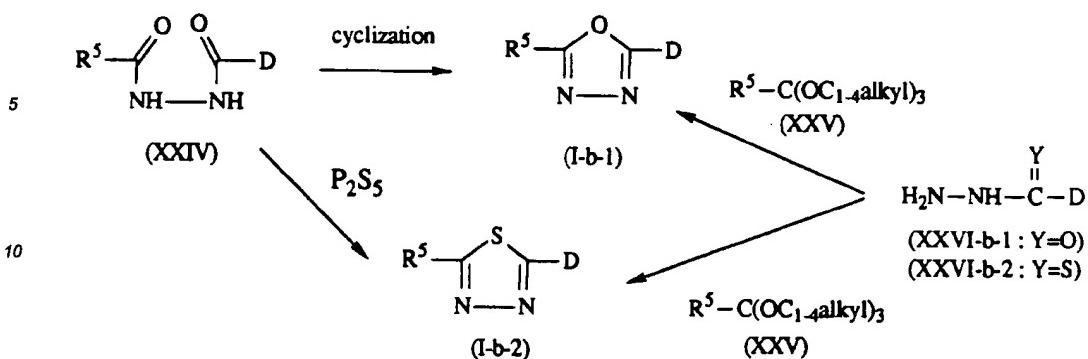
The compounds of formula (I) wherein Het is an oxazol, said compounds being represented by formula (I-a-1), can be prepared by cyclodehydration of an acylaminoketone of formula (XXI) in an appropriate reaction-inert solvent. Suitable dehydration reagents are, for example, sulfuric acid, phosphorus pentachloride, phosphorus pentoxide, phosphoryl chloride, thionyl chloride or a mixture of phosphoric acid or trifluoromethanesulfonic acid with acetic anhydride and the like.



The thiazolamines of formula (I), represented by formula (I-a-2), can be obtained by reaction between a thiourea (XXII) and an α -haloketone or an aldehyde of formula (XXIII) in a reaction-inert solvent. In formula (XXIII) W¹ represents a halo, e.g. fluoro, chloro, bromo or iodo.



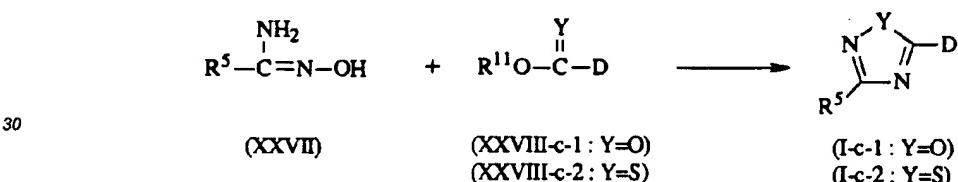
45 The compounds of formula (I), wherein Het is a 1,3,4-oxadiazol or a 1,3,4-thiadiazol, said compounds being
 represented by formula (I-b-1) and (I-b-2) respectively, can be prepared from diacylhydrazides of formula
 (XXIV). The cyclodehydration reaction to give the 1,3,4-oxadiazolamines of formula (I-b-1) can be carried out
 following the same procedures as described hereinbefore for the preparation of (I-a-1) from (XXI). The 1,3,4-
 50 thiadiazolamines of formula (I-b-2) can be obtained by reacting a diacylhydrazide of formula (XXIV) with phos-
 phorus pentasulfide in a suitable reaction-inert solvent.



15 Alternatively, the compounds of formula (I-b-1) and (I-b-2) can also be prepared by condensing a reactive hydrazide of formula (XXVI-b-1) or (XXVI-b-2) with an ortho ester of formula (XXV). Said reaction can be carried out by stirring and, if desired, heating the intermediate starting materials, either in an excess of said ortho ester or in a suitable reaction-inert solvent such as an ether, e.g. 1,1'-oxybisethane, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, and the like; an alcohol, e.g. methanol, ethanol, propanol, butanol and the like; or a mixture of such solvents.

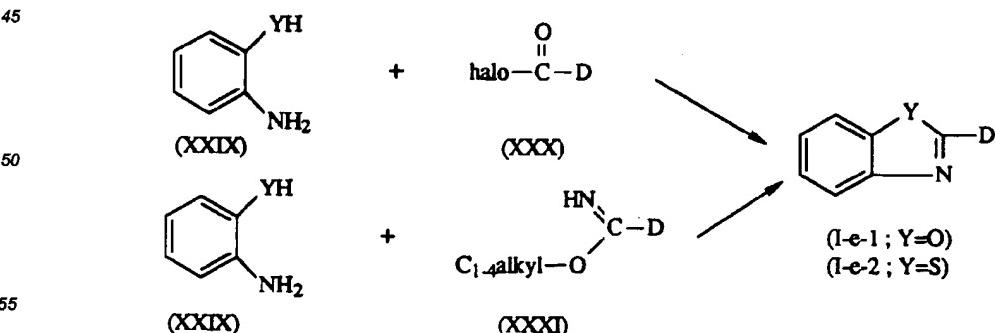
20 The compounds of formula (I) wherein Het is a 1,2,4-oxadiazolyl or a 1,2,4-thiadiazolyl of formula (c), said compounds being represented respectively by formula (I-c-1) and (I-c-2), can be prepared by reacting an intermediate of formula (XXVIII), wherein R¹¹ is hydrogen, C₁₋₄alkyl or aryl, with an amidoxime of formula (XXVII).

25



35 Said condensation reaction can be carried out as described hereinabove for the synthesis of (I-b) from (XXV) and (XXVI), optionally in the presence of an appropriate base such as, an alkoxide, hydride or amide, e.g. sodium methoxide, sodium hydride or sodium amide.

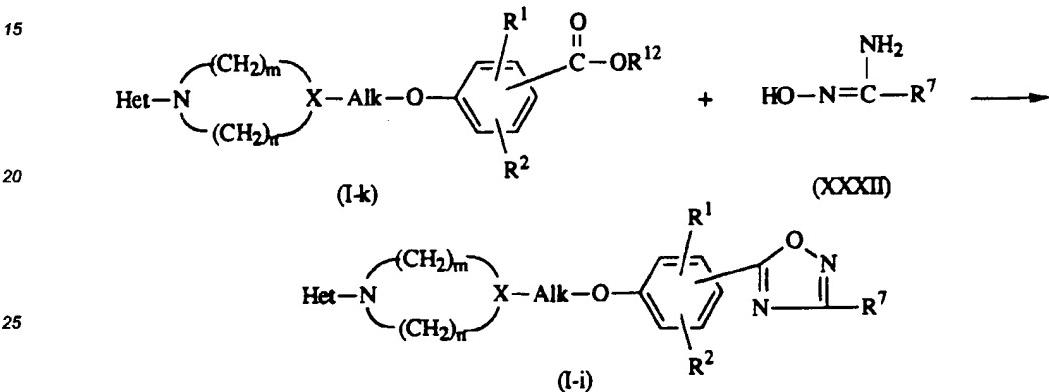
40 The compounds of formula (I) wherein Het is a benzoxazolyl or benzothiazolyl radical of formula (e), said compounds being represented by formula (I-e-1) and (I-e-2) respectively, can be prepared by reacting 2-amino(thio)phenol of formula (XXIX) with an acyl halide of formula (XXX). Alternatively said compounds can be obtained by reacting an imidate of formula (XXXI) with intermediate (XXIX). Both reactions can be carried out in an organic solvent such as for example, a halogenated hydrocarbon, e.g. dichloromethane, trichloromethane and the like; an alcohol, e.g. ethanol, 2-propanol and the like; an ether, e.g. 1,1'-oxybisethane, tetrahydrofuran, 1,4-dioxane and the like, or mixtures of such solvents.



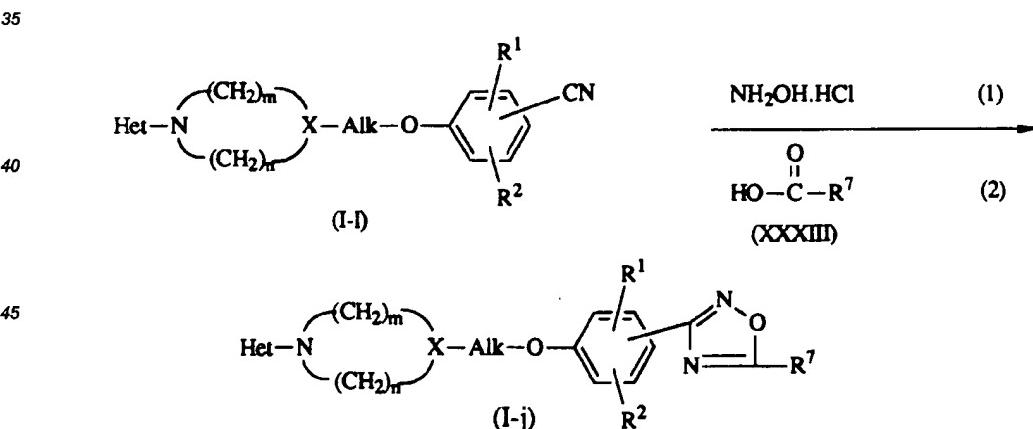
55 The compounds of formula (I) can also be converted into each other following art-known functional group transformation procedures.

The compounds of formula (I) wherein R³ is a substituted or unsubstituted 4,5-dihydro-2-oxazolyl radical of formula (f), said compounds being represented by formula (I-f) can be prepared following procedures described in EP-A-207,454 and EP-A-137,242. For example an appropriate acid, acyl halide or alkyl ester can be condensed with a substituted or unsubstituted hydroxalkylamine to give a hydroxalkylamide. The latter may in situ or, if desired, after isolating and purifying it, be cyclized by stirring with thionyl chloride or phosphorous trichloride optionally in the presence of a suitable inert solvent such as, an ether, e.g. tetrahydrofuran, 1,4-dioxane and the like, a halogenated hydrocarbon, e.g. trichloromethane, dichloromethane, an ester, e.g. ethyl acetate, isopropyl acetate and the like solvents.

10 The compounds of formula (I) wherein R³ is a 1,2,4-oxadiazol-5-yl-ring of formula (i), said compounds being represented by formula (I-i), can be prepared by reacting a compound of formula (I-k), wherein R¹² is hydrogen or C₁₋₄alkyl, with an amidoxime of formula (XXXII).



30 The compounds of formula (I) wherein R³ is a 1,2,4-oxadiazol-3-yl ring of formula (j), said compounds being represented by formula (I-j), can be prepared by reacting a compound of formula (I) wherein R³ is cyano, represented by formula (I-l), with hydroxylamine or an acid addition salt thereof and reacting the thus formed amidoxime with a carboxylic acid of formula (XXXIII) or a reactive functional derivative thereof such as, for example, a halide, an anhydride or an ortho ester form thereof.



50 The condensation reactions to prepare compounds (I-i) and (I-j) can be carried out by stirring and if desired heating the starting materials, neat or in a suitable reaction-inert solvent and optionally in the presence of an appropriate base such as, for example, an alkoxide, hydride or amide, e.g. sodium methoxide, sodium ethoxide, sodium hydride, sodium amide and the like. Suitable solvents for said condensation reactions are for example, ethers, e.g. 1,1'-oxybisethane, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane and the like; alkanols, e.g. methanol, ethanol, propanol, butanol and the like; or mixtures of such solvents. The water, acid or hydrohalic acid which is liberated during the condensation may be removed from the reaction mixture by azeotropic distillation, complexation, salt formation and the like methods.

The compounds wherein R³ is cyano may be hydrolysed thus yielding compounds of formula (I) wherein

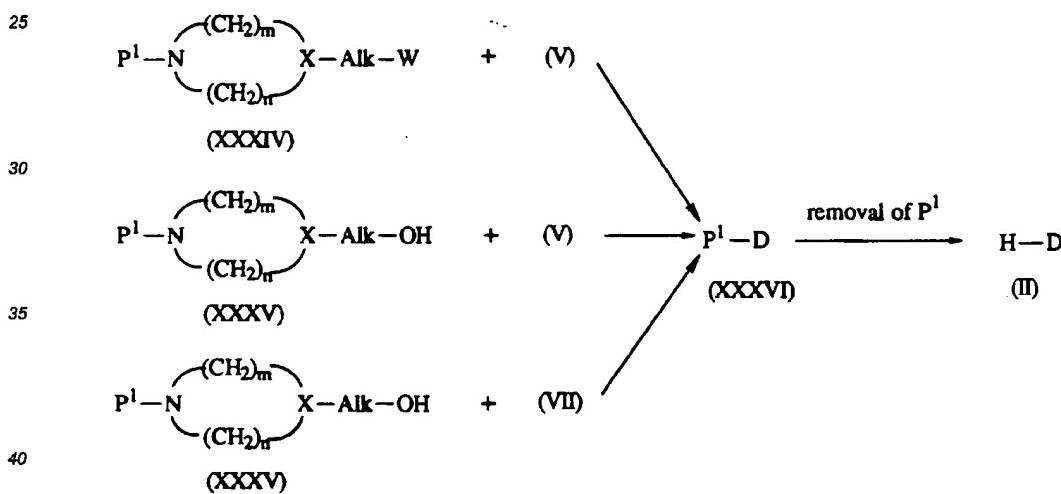
the radical R³ is a carboxyl group. Said hydrolysis reaction is preferably conducted in an aqueous acidic medium, e.g. in aqueous sulfuric, hydrochloric or phosphoric acid solution, at room temperature or at a slightly increased temperature. It may be advantageous to add a second acid to the reaction mixture, e.g. acetic acid.

The compounds of formula (I) wherein the radical R³ is a carboxyl group may be converted into the corresponding acyl halides by treatment with a suitable halogenating agent such as, for example, thionyl chloride, pentachlorophosphorane and sulfonyl chloride. Said acyl halides and said acids can further be derivatized to the corresponding esters by reacting said acids or acyl halides with a suitable alkanol following art-known esterification reaction procedures. Said reactions are most conveniently conducted in an appropriate solvent such as, for example, tetrahydrofuran, dichloromethane, trichloromethane, acetonitrile and the like solvents.

The compounds of formula (I) wherein the radical R³ is an ester group may be converted into the corresponding carboxylic acid following art-known saponification procedures, e.g. by treating the starting compound with an aqueous alkaline or an aqueous acidic solution.

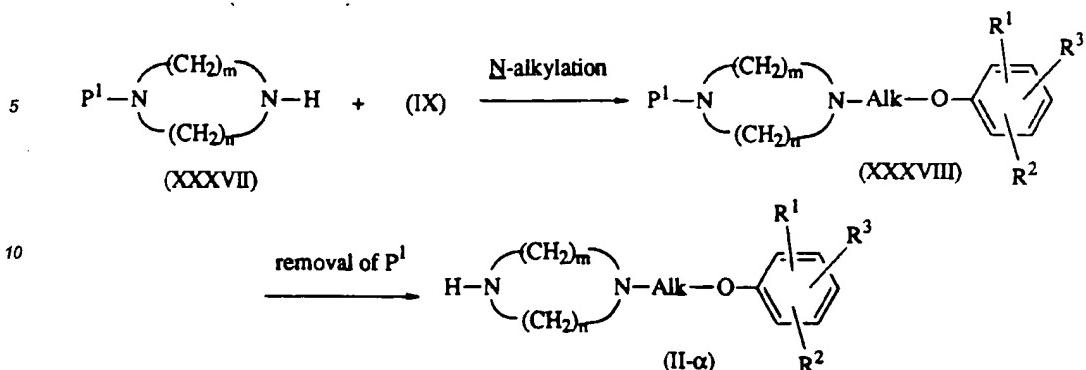
A number of intermediates and starting materials in the foregoing preparations are known compounds which may be prepared according to art-known methodologies of preparing said or similar compounds and some intermediates are new. A number of such preparation methods will be described hereinafter in more detail.

In the next reaction scheme there are mentioned some different ways of preparing intermediates of formula (XXXVI), which can be converted into intermediates of formula (II) by removing the protective group P¹. The symbol P¹ represents a suitable protective group which is readily removable by hydrogenation or hydrolysis. Preferred protective groups may be, for example, hydrogenolyzable groups e.g. phenylmethyl, phenyl-methoxycarbonyl and the like, or hydrolyzable groups, e.g. C₁₋₄alkylcarbonyl, C₁₋₄alkylphenylsulfonyl and the like.

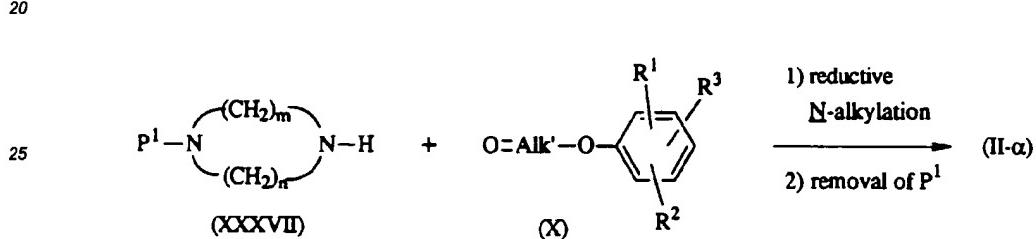


The intermediates of formula (XXXVI) can be prepared by O-alkylating a phenol of formula (V) with a reagent of formula (XXXIV), by reacting the phenol (V) with an alcohol of formula (XXXV) or alternatively by O-alkylating an alcohol of formula (XXXV) with an appropriate reagent of formula (VII), following the same methods as described hereinbefore for the preparation of (I).

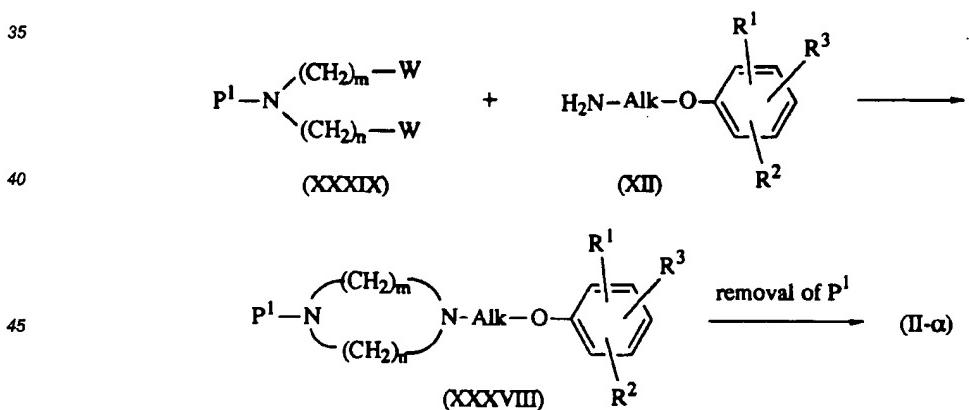
The intermediates of formula (II) wherein X is N, said intermediates being represented by (II- α), can be prepared by N-alkylating an amine of formula (XXXVII) with a reagent of formula (IX), following N-alkylation procedures as described hereinbefore, and subsequently removing the protective group P¹ in the thus obtained intermediate (XXXVIII).



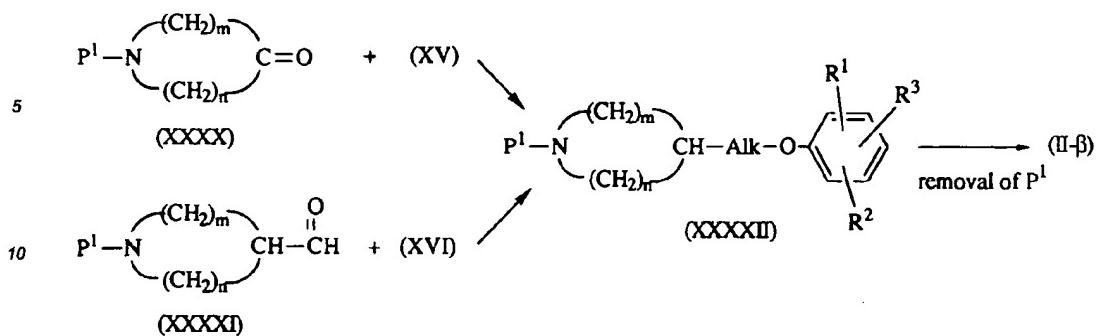
The intermediates of formula (II- α) can alternatively be prepared by reductive N-alkylating an intermediate of formula (XXXVII) with a ketone or aldehyde of formula (X) following art-known N-alkylation procedures as described hereinbefore for the synthesis of (I- α) starting from (VIII) and (X) and subsequently removing the protective group P1 in the thus obtained intermediate.



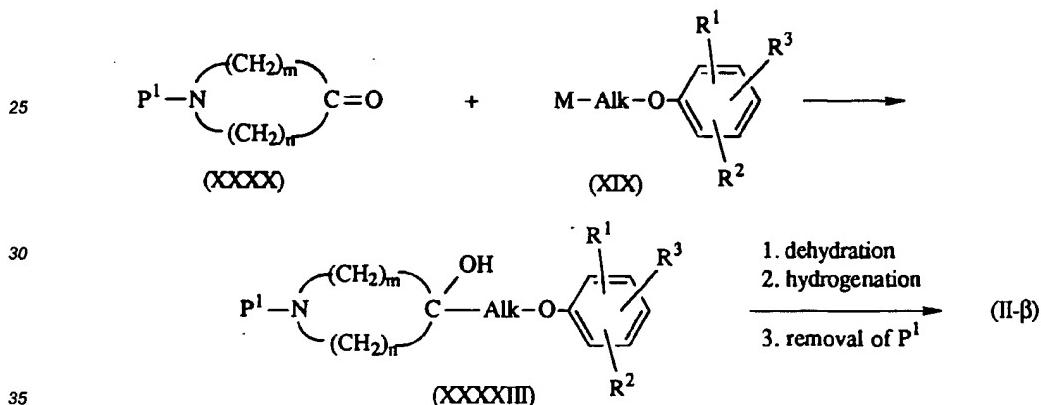
30 Additionally the intermediates of formula (II- α) may be prepared by cyclizing an intermediate of formula (XXXIX) with an amine of formula (XII) as described hereinbefore for the preparation of (I- α) from (XI) and (XII) and subsequently removing the protective group P¹ in the thus obtained intermediate (XXXVIII).



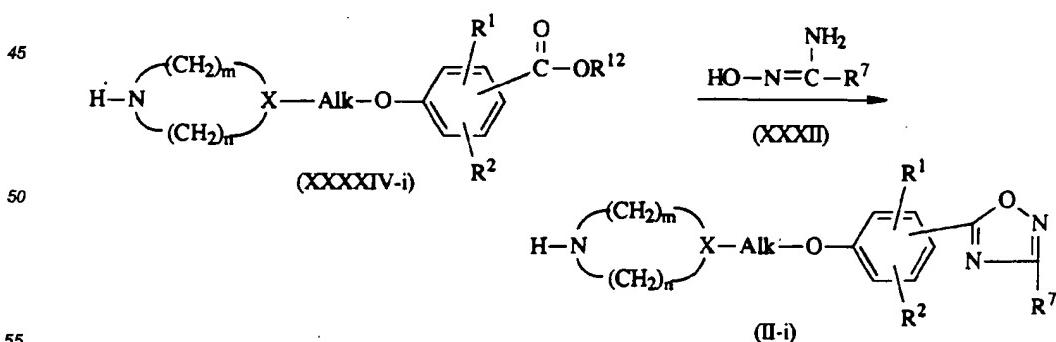
50 Intermediates of formula (II) wherein X is CH, said intermediates being represented by formula (II- β), may also be prepared by reacting a ketone of formula (XXXX) with an ylide of formula (XV) or by reacting an aldehyde (XXXXI) with an ylide of formula (XVI). Reduction of the thus obtained intermediates gives intermediates of formula (XXXXII) as described hereinbefore for the preparation of (I- β). Removal of the protective group P1 in (XXXXII) yields the intermediates of formula (II- β).



- 15 Alternatively, the intermediates of formula (II- β) may be prepared by reacting a ketone of formula (XXXX) with an organometallic reagent of formula (XIX). The thus prepared alkanol of formula (XXXXIII) may subsequently be dehydrated and hydrogenated as described hereinbefore for the preparation of (I- β) from (XIII) and (XIX). Removal of the protective group P^1 in (XXXXIII) yields intermediates of formula (II- β). In a similar way an aldehyde of formula (XXXXI) may also be reacted with an organometallic reagent, dehydrated and reduced to yield a compound of formula (II- β), after removal of the protective group P^1 .



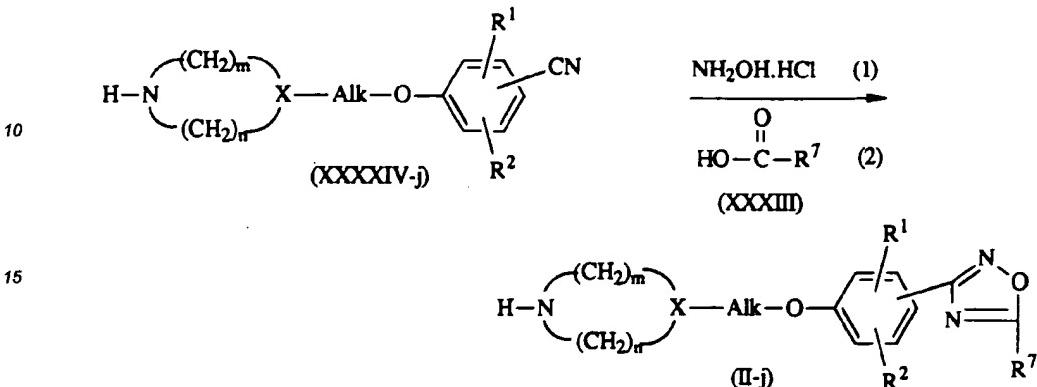
- 40 The intermediates of formula (II) wherein R^3 is a heterocycle of formula (f), (g), (i) or (j), can also be prepared by cyclizing an appropriate piperidinyl, pyrrolidinyl or piperazinyl alkylphenol ether (XXXIV). For example, the intermediates of formula (II) wherein R^3 is a 1,2,4-oxadiazol-5-yl ring of formula (i), said intermediates being represented by formula (II-i), can also be prepared by reacting an intermediate of formula (XXXIV-i) with an amidoxime of formula (XXXII) as described hereinbefore for the preparation of (I-i) from (I-m) and (XXXII).



The intermediates of formula (II) wherein R^3 is a 1,2,4-oxadiazol-3-yl ring of formula (j), said intermediates being represented by formula (II-j), can be obtained by reacting an intermediate of formula (XXXIV-j) with hydroxylamine or an acid addition salt thereof and reacting the thus formed intermediate with a carboxylic acid

of formula (XXXIII) or a functional derivative thereof, such as, for example, a halide, an anhydride or an ortho ester form thereof. The reaction can be carried out following the same procedure as described for the synthesis of (I-j) from (I-n) and (XXXIII).

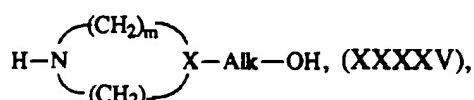
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Intermediates of formula (IV) can be prepared by N-alkylating a heterocycle of formula (III) with an amine of formula

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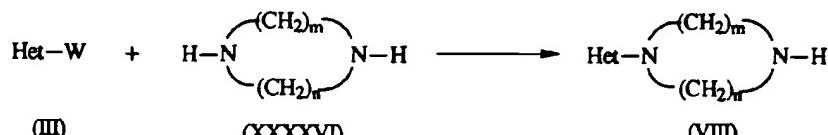
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following art-known N-alkylation procedures and subsequently converting the alcohol function of the thus obtained intermediate (VI) into an appropriate leaving group with an appropriate halogenating agent such as, for example, thionyl chloride, sulfonyl chloride, pentachlorophosphorane, pentabromophosphorane or an appropriate sulfonyl halide such as, for example, methanesulfonyl chloride or 4-methylbenzenesulfonyl chloride.

35

The intermediates of formula (VIII) can be obtained by reacting intermediates of formula (XXXXVI) with a heterocycle of formula (III) following art-known N-alkylation procedures as described hereinbefore.

40



45

Intermediates of formula (III), wherein Het is a radical of formula (a), said intermediates being represented by formula (III-a) can be obtained by reacting the amine of formula (XXXXVII) with an alkali metal nitrite, e.g. sodium nitrite, in an aqueous acidic medium to obtain a diazonium salt. This salt is treated with an alkali metal halide, e.g. sodium chloride, sodium bromide thus obtaining the intermediates of formula (III-a).

50



55

Starting materials and intermediates used in all of the preceding procedures for which no specific preparation is given herein, may be prepared according similar procedures as described hereinbefore for compounds of formula (I), and/or may be prepared following art-known methodologies described in the literature for the preparation of similar known compounds. For example, intermediates of formula (V) and (IX) wherein R³ is a substituted or unsubstituted 4,5-dihydro-2-oxazolyl radical may be prepared following similar procedures de-

scribed in EP-A-137,242 and EP-A-207,454.

The compounds of formula (I) and some of the intermediates in this invention may have an asymmetric carbon atom in their structure. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Alternatively, enantiomerically pure compounds and intermediates may also be obtained by chromatography of the racemate over a chiral stationary phase and the like techniques. Pure stereochemically isomeric forms of the compounds of formula (I) may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

The compounds of formula (I) and the pharmaceutically acceptable addition salts and stereoisomeric forms show antiviral activity and are particularly attractive due to their favourable therapeutic index, resulting from an acceptable low degree of cell toxicity, combined with satisfactory antiviral activity. The antiviral properties of the compounds of formula (I) can be demonstrated for example in the "Picornavirus Minimal Inhibitory Concentration (MIC)"-test, illustrating the useful antiviral activity of the compounds of the present invention.

The compounds of the present invention are therefore useful agents for inhibiting the growth and/or replication of viruses. The compounds of formula (I), the pharmaceutically acceptable addition salts and stereochemically isomeric forms thereof are active against a broad spectrum of picornaviruses, including enteroviruses e.g. Coxsackieviruses, Echoviruses, Enteroviruses, e.g. Enterovirus 70 and especially numerous strains of rhinoviruses, e.g. Human Rhinovirus serotypes HRV -2,-3,-4,-5,-6,-9,-14,-15,-29,-39,-42,-45,-51,-59,-63,-70,-72,-85,-86 and the like.

In view of their potent, local as well as systemic, antiviral activity the compounds of this invention constitute useful tools for inhibiting, combating or preventing the growth of viruses. More particularly these compounds may be used as medicines against viral diseases, especially respiratory diseases e.g. common cold, pneumonia, bronchiolitis, herpangina and the like, CNS-diseases e.g. paralysis, aseptic meningitis, encephalitis and the like, cardiac disease e.g. pericarditis, myocarditis and the like, hepatic diseases e.g. hepatitis and the like, gastrointestinal diseases e.g. diarrhea and the like, ophtalmic diseases e.g. acute hemorrhagic conjunctivitis and the like, dermatological diseases e.g. exanthem, rash, hand-foot-and-mouth disease, and the like diseases. Said use as a medicine comprises the systemic or topical administration to warm-blooded animals of an antivirally effective amount of a compound of formula (I), a pharmaceutically acceptable addition salt or a stereoisomeric form thereof. Some compounds of the invention are especially useful to treat respiratory diseases, like common cold due to their prolonged in vivo activity in the buccal and nasal cavity.

The subject compounds may be formulated into various pharmaceutical forms for systemic or topical administration purposes. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, intranasally, by parenteral injection or for ophtalmic administration. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or

may be helpful for preparing the desired compositions. These compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch or the matrix or reservoir type as are conventional in the art for this purpose.

- 5 In the compositions suitable for topical administration the active ingredient will preferably be a semisolid such as a thickened composition such as salves, creams, gellies, ointments and the like which can be applied by a swab. Pharmaceutical composition suitable for topical administration may also be in form of drops, lotions or an aerosol. Suitable aerosol preparations may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas. Addition salts of (I) due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

In a further aspect of the invention there are provided particular pharmaceutical compositions which comprise a compound of formula (I), a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof and a cyclodextrin or a derivative thereof. When applied to the site of infection such cyclodextrin based compositions result in a continuous and controlled delivery of sufficiently high concentrations of the antiviral compound of formula (I) to the site of the infection for sustained periods of time.

Such compositions are particularly convenient for treating local viral infections, in particular mucosal infections, e.g. nasal or eye infections.

The cyclodextrin to be used in the aforementioned compositions include the pharmaceutically acceptable unsubstituted and substituted cyclodextrins known in the art, more particularly α , β or γ -cyclodextrins or the pharmaceutically acceptable derivatives thereof.

Substituted cyclodextrins which can be used in the invention include polyethers described in U.S. Patent 3,459,731 which is incorporated by reference for the definition and processes for preparation. In general, unsubstituted cyclodextrins are reacted with an alkylene oxide, preferably under superatmospheric pressure and at an elevated temperature, in the presence of an alkaline catalyst.

Since a hydroxy moiety of the cyclodextrin can be substituted by an alkylene oxide which itself can react with yet another molecule of alkylene oxide, the average molar substitution (MS) is used as a measure of the average number of moles of the substituting agent per glucose unit. The MS can be greater than 3 and theoretically has no limit.

Further substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-6} alkyl, hydroxy C_{1-6} alkyl, carboxy C_{1-6} alkyl or C_{1-6} alkyloxycarbonyl C_{1-6} alkyl or mixed ethers thereof. In particular such substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-3} alkyl, hydroxy C_{2-4} alkyl or carboxy C_{1-2} alkyl or more in particular by methyl, ethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, carboxymethyl or carboxyethyl.

In the foregoing definitions the term " C_{1-6} alkyl" is meant to include straight and branched saturated hydrocarbon radicals, having from 1 to 6 carbon atoms, such as, methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, 2-methylpropyl, butyl, pentyl, hexyl and the like.

Such ethers can be prepared by reacting the starting cyclodextrin with an appropriate $\text{O-alkylating agent}$ or a mixture of such agents in a concentration being selected so that the desired cyclodextrin ether is obtained.

40 The said reaction is preferably conducted in a suitable solvent in the presence of an appropriate base. With such ethers, the degree of substitution (DS) is the average number of substituted hydroxy functions per glucose unit, the DS being thus 3 or less.

In the cyclodextrin derivatives for use in the compositions according to the present invention, the DS preferably is in the range of 0.125 to 3, in particular 0.3 to 2, more in particular 0.3 to 1 and the MS is in the range of 0.125 to 10, in particular of 0.3 to 3 and more in particular 0.3 to 1.5.

Other references describing cyclodextrins for use in the compositions according to the present invention, and which provide a guide for the preparation and characteristics of cyclodextrins, for the process of depositing the selected agent within the cavity of the cyclodextrin molecule and for the use of cyclodextrins in pharmaceutical compositions, include the following:

50 "Cyclodextrin Technology" by József Szejtli, Kluwer Academic Publishers (1988) in the chapter Cyclodextrins in Pharmaceuticals; "Cyclodextrin Chemistry" by M.L. Bender et al., Springer-Verlag, Berlin (1978); Advances in Carbohydrate Chemistry", Vol. 12 Ed. by M.L. Wolfrom, Academic Press, New York (157) in the chapter The Schardinger Dextrans by Dexter French at p. 189-260; "Cyclodextrins and their Inclusions Complexes" by J. Szejtli, Akadémiai Kiadó, Budapest, Hungary (1982); I. Tabushi in Acc. Chem. Research, 1982, 15, p. 66-72; W. Sanger, Angewandte Chemie, 92, p. 343-361 (1981); A. P. Croft and R. A. Bartsch in Tetrahedron, 39, p. 1417-1474 (1983); German Offenlegungsschrift DE 3118218; German Offenlegungsschrift DE 3317064; EP-A-94,157; EP-A-149,197; U.S. Patent 4,659,696; and U.S. Patent 4,383,992.

Of particular utility in the invention are the β -cyclodextrin ethers, e.g. dimethyl- β -cyclodextrin as described

in Drugs of the Future, Vol. 9, No. 8, p. 577-578 by M. Nogradi (1984) and polyethers, e.g. hydroxypropyl β -cyclodextrin and hydroxyethyl β -cyclodextrin, being examples. Such an alkyl ether may be a methyl ether with a degree of substitution of about 0.125 to 3, e.g. about 0.3 to 2. Such a hydroxypropyl cyclodextrin may for example be formed from the reaction between β -cyclodextrin and propylene oxide and may have a MS value of about 0.125 to 10, e.g. about 0.3 to 3.

5 In said particular cyclodextrin based formulation, the molecules of the antiviral compounds of formula (I) are surrounded, at least in part, by the cyclodextrin, i.e. the agent fits into the cyclodextrin cavity.

10 To prepare said particular cyclodextrin based pharmaceutical compositions of the invention, the selected antiviral compound (or compounds) of formula (I), the pharmaceutically acceptable addition salt of the stereochemically isomeric form thereof is deposited within the cyclodextrin molecule itself, such process being known in the art for other active agents. In the final compositions, the molar ratio of cyclodextrin:antiviral compound is from about 1:1 to about 5:1, in particular, about 1:1 to about 2:1. Thus, in general, the composition will be prepared by dissolving the cyclodextrin in water and adding the antiviral compound to this solution, preferably under vigorous stirring and preferably at a temperature in the range of 10°C to 50°C, in particular in range of 15°C to 30°C, and preferably at room temperature.

15 In the final compositions, the cyclodextrin will comprise about 2.5 to 40% by weight, in particular about 2.5 to 25%, more in particular 5 to 25%, or 5 to 20%, for example about 10%, with the remainder being water, preservative, the active ingredient and any excipients.

20 In particular, the pharmaceutical compositions may consist only of water, cyclodextrin and the antiviral agents without the need for co-solvents such as ethanol or surfactants.

25 Application of the cyclodextrin based compositions of the invention may be by aerosol, e.g. with a propellant such as nitrogen, carbon dioxide, a freon, or without a propellant such as a pump spray, drops, or a semisolid such as a thickened compositions which can be applied by a swab. In particular applications, semisolid compositions such as salves, creams, gellies, ointments and the like will conveniently be used.

30 For the liquid preparations of said cyclodextrin based compositions, any of the usual pharmaceutical media may be added, such as, for example, glycols, oils, alcohols and the like, however in concentrations below the level of irritation. In order to stabilize the formulations the pH may be increased or decreased or stabilized by adding appropriate acids, bases or buffer systems, e.g. citrate, phosphate buffers. Further additives may comprise substances to make the formulations isotonic, e.g. sodium chloride, mannitol, glucose and the like. It is further recommendable to add a preservative to the formulations such as, for example, a mercury salt or complex salt, e.g. phenyl mercuriacetate, nitrate, chloride or borate, phenylethyl alcohol, ethanol, propylene glycol and the like. Suitable thickeners for obtaining the above-mentioned thickened compositions comprise polyvinyl alcohols, hydroxypropyl methyl celluloses, hydroxyethyl celluloses, methylcelluloses, polyvinyl pyrrolidone, acrylic acid polymers and the like.

35 Depending on the type of virus which is to be controlled, said cyclodextrin based compositions can be applied in the vagina, nose, mouth, eyes, lungs or within the cheeks so as to control viruses which have not entered the blood stream of the patient, e.g. viruses which are located in mucous membranes of the body. The cyclodextrin based compositions of the invention are particularly useful on those infection sites where the natural defense mechanisms prevent the delivery of antiviral agents during sustained periods due to an effective elimination of the active compound from the site of infection. Such elimination may be due to clearance by ciliary movement or secretion, or by absorption.

40 As part of the pharmaceutical composition, one may also include the same or a different active antiviral in a different delivery carrier so as to provide a different profile of activity, e.g. a wide range of time during 45 which the composition shows activity or a supplement to bolster a low level at a particular point in the release schedule of the cyclodextrin.

45 It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, drops, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

50 Those of skill in treating antiviral diseases in warm-blooded animals could easily determine the effective amount from the test results presented hereinafter. In general it is contemplated that an effective amount would be from 0.001 mg/kg to 50 mg/kg body weight, preferably from 0.01 mg/kg to 10 mg/kg body weight.

55 The following examples are intended to illustrate the scope of the present invention in all its aspects. Unless otherwise stated all parts therein are by weight.

EXPERIMENTAL PARTA. Preparation of the intermediates

5

Example 1

- a) To a cooled (ice-bath) mixture of 62.4 parts of a dispersion of sodium hydride in mineral oil (50%) and 1520 parts of 1,2-dimethoxyethane were added portionwise 270 parts of diethyl [(ethoxycarbonyl)methyl]phosphonate, keeping the temperature below 15°C. After stirring for 2 hours, there were added portionwise 228 parts of 1-(phenylmethyl)-4-piperidinone (temp. <15°C) under a nitrogen atmosphere. Stirring was continued for 2 hours at room temperature and for 1 hour at 40°C. After cooling, the reaction mixture was diluted with water. The aqueous layer was separated and extracted with 1,1'-oxybisethane. The combined organic layers were dried, filtered and evaporated. The residue was converted into the hydrochloride salt in 1,1'-oxybisethane. The salt was recrystallized from 2-propanone, yielding 260.0 parts of ethyl [1-(phenylmethyl)-4-piperidinylidene]acetate hydrochloride; mp. 186-190.5 (interm. 1).
- b) A mixture of 302 parts of intermediate 1 and 2000 parts of acetic acid was hydrogenated at normal pressure and at 24-36°C with 4 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was washed with 1,1'-oxybisethane and basified with NaOH. The product was extracted with 1,1'-oxybisethane and the extract was dried, filtered and evaporated. The residual oil was distilled in vacuo. The product was converted into the hydrochloride salt in a mixture of 1,1'-oxybisethane and ethanol. After evaporazation of the solvent, the salt was filtered off and dried, yielding 41 parts of ethyl [1-(phenylmethyl)-4-piperidinyl]acetate hydrochloride; mp. 122.5-137°C (decomp.) (interm. 2).
- c) To a suspension of 4.57 parts of lithium aluminum hydride in 240 parts of 1,1'-oxybisethane was added dropwise a solution of 30 parts of intermediate 2 in 120 parts of 1,1'-oxybisethane. After stirring for 10 hours at reflux temperature and subsequent cooling, the reaction mixture was diluted with water and basified with NaOH. The whole was filtered and the filtrate was evaporated. The residue was distilled in vacuo, yielding 20 parts of 1-(phenylmethyl)-4-piperidineethanol; bp. 154-156°C at 60 Pa (interm. 3).
- d) To a cooled (-10°C) mixture of 19.6 parts of triphenyl phosphine in 53.4 parts of tetrahydrofuran were added portionwise 13.7 parts of diethyl azodicarboxylate. After stirring for 15 min., there was added a solution of 16.5 parts of intermediate 3 and 12.5 parts of ethyl 4-hydroxybenzoate in 53.4 parts of tetrahydrofuran, keeping the temperature between -5°C and 0°C. Stirring was continued overnight at room temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was crystallized from 2,2'-oxybispropane and was then converted into the (Z)-2-butenedioate salt in 2-propanol. The product was filtered off and dried, yielding 15 parts (41.3%) of ethyl 4-[2-[1-(phenylmethyl)-4-piperidinyl]ethoxy]benzoate (Z)-2-butenedioate(1:1); mp. 142.0°C (interm. 4).
- e) A mixture of 4.8 parts of intermediate 4 and 119 parts of ethanol was hydrogenated at normal pressure and 50°C with 2 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was crystallized from 2-propanol, yielding 4.5 parts (100%) of ethyl 4-[2-(4-piperidinyl)ethoxy]benzoate butanedioate(1:1); mp. 146.7°C (interm. 5).

45

Example 2

- a) A mixture of 16 parts of 1-bromo-3-chloropropane, 16 parts of 2-chloro-4-methoxyphenol, 20 parts of potassium carbonate and 200 parts of 2-propanone was stirred overnight at reflux temperature. The reaction mixture was filtered and the filtrate was evaporated, yielding 18 parts (75%) of 2-chloro-1-(3-chloropropoxy)-4-methoxybenzene (interm. 6).
- b) A mixture of 3.16 parts of ethyl 1-piperazinecarboxylate, 4.7 parts of intermediate 6, 3.2 parts of sodium carbonate and 67.5 parts of N,N-dimethylformamide was stirred overnight at reflux temperature. After cooling, the reaction mixture was poured into water and the product was extracted with 2,2'-oxybispropane. The extract was dried, filtered and evaporated and the residue was converted into the hydrochloride salt in 2,2'-oxybispropane. The product was filtered off and dried, yielding 4 parts (50%) of ethyl 4-[3-(2-chloro-4-methoxyphenoxy)propyl]-1-piperazinecarboxylate monohydrochloride (interm. 7).
- c) A mixture of 3.56 parts of intermediate 7, 3.6 parts of potassium hydroxid and 80 parts of 2-propanol was stirred overnight at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane and the extract was dried, filtered and

5 evaporated. The residue was converted into the hydrochloride salt in 2-propanol. The salt was recrystallized from 2-propanol, filtered off and dried, yielding 1.33 parts (37.1%) of 1-[3-(2-chloro-4-methoxyphenoxy)propyl]piperazine dihydrochloride; mp. 190°C (interm. 8). In a similar manner there was also prepared: 1-[2-(2-chloro-4-methoxyphenoxy)ethyl]piperazine dihydrochloride; mp. 210°C (interm. 9).

Example 3

10 A mixture of 224 parts of piperazine, 97 parts of ethyl 4-(3-chloropropoxy)benzoate and 1044 parts of methylbenzene was stirred overnight at reflux temperature. After cooling, the organic layer was washed three times with water, dried, filtered and evaporated, yielding 115.2 parts (98.5%) of ethyl 4-[3-(1-piperazinyl)pro-
15 poxy]benzoate as a residue (interm. 10).

In a similar manner there was also prepared:

15 ethyl 4-[2-(1-piperazinyl)ethoxy]benzoate (interm. 11).

Example 4

20 a) A mixture of 32 parts of ethyl 1-piperazinecarboxylate, 17 parts of 3-chloro-1,2-benzisothiazole and 45 parts of *N,N*-dimethylacetamide was stirred for 0.5 hour at 150°C. After cooling to 50°C, the reaction mixture was poured into ice water. The aqueous layer was decanted and the oily layer was stirred again in water. The product from the oily layer was extracted with trichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated, yielding 13 parts (44%) of ethyl 4-(1,2-benzisothiazol-3-yl)-1-piperazinecarboxylate as a residue (interm. 12).

25 b) A mixture of 12.5 parts of intermediate 12 and 187.5 parts of a hydrobromic acid solution 48% in water was stirred for 1.5 hour at reflux temperature. After evaporation, the residue was taken up in 2-propanol and the solvent was evaporated again. The residue was dissolved in methanol, evaporated again and stirred in 2-propanone. The product was filtered off and dried, yielding 11.5 parts (73%) of 3-(1-piperazinyl)-1,2-benzisothiazole dihydribromide (interm. 13).

Example 5

30 a) To a cooled (0°C) solution of 13.5 parts of trichloromethyl carbonochloridate in 130 parts of dichloromethane was added dropwise a solution of 28.2 parts of intermediate 5 and 10.3 parts of *N,N*-diethylethanamine in a small amount of dichloromethane. Upon complete addition, the reaction mixture was stirred for 3 hours at room temperature. The whole was poured into a mixture of ice water and trichloromethane. The separated organic layer was dried, filtered and evaporated, yielding 40 parts (100%) of ethyl 4-[2-[1-(chlorocarbonyl)-4-piperidinyl]ethoxy]benzoate as a residue (interm. 14).

35 b) To a stirred solution of 3 parts of hydrazine monohydrate in 45 parts of tetrahydrofuran was added dropwise a solution of 8.5 parts of intermediate 14 in 45 parts of tetrahydrofuran at room temperature. Upon complete addition, stirring was continued for 3 hours. The reaction mixture was poured into water and the product was extracted with trichloromethane. The extract was dried, filtered and evaporated. The residue was crystallized from 2-propanol. The product was filtered off and dried at 60°C, yielding 3.5 parts (41.7%) of ethyl 4-[2-[1-[(hydrazinocarbonyl)-4-piperidinyl]ethoxy]benzoate; mp. 131.2°C (interm. 15).

40 c) To a stirred mixture of 6.7 parts of intermediate 15, 4.2 parts of sodium carbonate and 150 parts of trichloromethane were added dropwise 2.8 parts of acetic acid anhydride. Upon complete addition, stirring was continued for 2 days at room temperature. The reaction mixture was filtered, washed with trichloromethane and the filtrate was evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The desired fractions were collected and the eluent was evaporated. The residue was crystallized from 2-propanol and dried at 50°C, yielding 6.4 parts (84.8 %) of ethyl 4-[2-[1-(2-acetylhydrazino)carbonyl]-4-piperidinyl]ethoxy]benzoate; mp. 161.5°C (interm. 16).

Example 6

50 a) A mixture of 9.8 parts of 2,5-dibromo-1,3,4-thiadiazole, 4.6 parts of 3-pyrrolidin ethanol, 5.3 parts of sodium carbonate and 141 parts of *N,N*-dimethylformamide was stirred overnight at 60°C. The reaction mixture was evaporated and the residue was taken up in water and dichloromethane. The separated or-

ganic layer was dried, filtered and vaporat d, yielding 11 parts (98.8%) of 1-(5-bromo-1,3,4-thiadiazol-2-yl)-3-pyrrolidineethanol as a residue (interm. 17).

5 b) A solution of 11 parts of intermediate 17 in 195 parts of dichloromethane was added dropwise to 16.6 parts of thionyl bromide at room temperature. Upon complete addition, the reaction mixture was stirred overnight at room temperature. The precipitated product was filtered off, washed with dichloromethane and 2,2'-oxybispropane and dried at 60°C, yielding 10.7 parts (85.5%) of 2-bromo-5-[3-(2-bromoethyl)-1-pyrrolidinyl]-1,3,4-thiadiazole monohydrobromide (interm. 18).

10 Example 7

To a stirred and cooled (-10°C) solution of 13.9 parts of 5-phenyl-2-thiazolamine (this product is described in J. Am. Chem. Soc. 71, 4007, 1949) and 119 parts of phosphoric acid were added dropwise 37.5 parts of nitric acid. Upon complete addition, a solution of 7.85 parts of sodium nitrite in 12.4 parts of water was added dropwise during 35 minutes at -5°C. Upon completion, the thus obtained solution was added dropwise to a cooled (-5°C) mixture of 13.2 parts of copper(II)sulfate, 51.4 parts of sodium bromide and 275 parts of water. Upon completion, the reaction mixture was allowed to stand overnight to reach room temperature. The whole was neutralized with sodium carbonate (exothermic reaction, the temperature rose to 40°C). After cooling, the product was extracted with dichloromethane. The extract was dried, filtered and evaporated, yielding 18.6 parts (98.0%) of 2-bromo-5-phenylthiazole as a residue (interm. 19).

20 B. Preparation of the Final compounds

25 Example 8

A mixture of 3 parts of 2-bromo-5-methyl-1,3,4-thiadiazole, 4.8 parts of intermediate 5, 5.3 parts of sodium carbonate and 0.94 parts of *N,N*-dimethylformamide was stirred for 6 hours at 160°C. After cooling, the reaction mixture was partitioned between water and dichloromethane. The organic layer was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (99.5:0.5 by volume) as eluent. The eluent of the desired fraction was evaporated and the residue was crystallized from 2-propanol, yielding 3.4 parts (60.4%) of ethyl 4-[2-[1-(5-methyl-1,3,4-thiadiazol-2-yl)-4-piperidinyl]ethoxy]benzoate; mp. 98.5°C (compound 13).

35 Example 9

A mixture of 3.5 parts of ethyl 2-bromo-4-thiazolecarboxylate, 4.5 parts of intermediate 11 and 1.6 parts of sodium carbonate was stirred for 5 hours at 160°C. After cooling, the reaction mixture was poured into a mixture of water and trichloromethane. The separated organic layer was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The desired fraction was collected and the eluent was evaporated. The residue was crystallized from 2,2'-oxybispropane, yielding, after drying at 50°C, 2.2 parts (33.8%) of ethyl 2-[4-[2-[4-(ethoxycarbonyl)phenoxy]ethyl]-4-thiazolecarboxylate; mp. 88.5°C (compound 34).

45 Example 10

A mixture of 3.05 parts of 2-chlorobenzothiazole, 4.2 parts of intermediate 11, 3.2 parts of sodium carbonate and 47 parts of *N,N*-dimethylformamide was stirred for 7 hours at 140°C. After cooling, the reaction mixture was poured into water and the product was extracted with methylbenzene. The extract was washed with water, dried, filtered and evaporated. The residue was crystallized from 2-propanol. The product was filtered off, washed and dried in vacuo at 50°C, yielding 5.4 parts (87.5%) of ethyl 4-[2-[4-(2-benzothiazolyl)-1-piperazinyl]ethoxy]benzoate; mp. 119.6°C (compound 46).

55 Example 11

A mixture of 4.5 parts of intermediate 11, 6.6 parts of sodium carbonate and 80 parts of 4-methyl-2-p-nanone was refluxed for 30 minutes using a water separator. After cooling to 40°C, 3.9 parts of 3-chloro-1,2-benzisothiazole, 1,1-dioxide were added and stirring was continued overnight at reflux temperature. The reaction mixture was cooled and water was added. The precipitate was filtered off, washed with water and 4-methyl-2-pentanone and dissolved in dichloromethane. The separated 4-methyl-2-pentanone layer from the filtrat

was washed, dried, filtered and evaporated. The dichloromethane layer was washed, dried, filtered and evaporated. The combined residues were crystallized from 2-propanol. The product was filtered off, washed and dried in vacuo at 60°C, yielding 5.4 parts (76.1%) of ethyl 4-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethoxy]benzoate, 1,1-dioxide; mp. 143.6°C (compound 23).

Example 12

A mixture of 6.2 parts of 3-chloro-1,2-benzisothiazole, 9.8 parts of intermediate 5, 4.2 parts of sodium carbonate and 0.2 parts of potassium iodide was stirred for 4 hours at 150°C. After cooling, the mixture was poured into water and the product was extracted with dichloromethane. The extract was washed, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using trichloromethane as eluent. The desired fraction was collected and the eluent was evaporated. The residue was crystallized from 2-propanol. The product was filtered off, washed and dried in vacuo at 50°C, yielding 2.5 parts (16.9%) of ethyl 4-[2-[1-(1,2-benzisothiazol-3-yl)-4-piperidinyl]ethoxy]benzoate; mp. 103.3°C (compound 19).

Example 13

A mixture of 2.3 parts of 2-chlorobenzoxazole, 4.7 parts of intermediate 5, 4.2 parts of sodium hydrogen carbonate and 79 parts of ethanol was stirred overnight at reflux temperature. The reaction mixture was evaporated and the residue was partitioned between water and dichloromethane. The organic layer was dried, filtered and evaporated and the residue was crystallized from 2-propanol. The product was dried at 50°C, yielding 3.4 parts (57.5%) of ethyl 4-[2-[1-(2-benzoxazolyl)-4-piperidinyl]ethoxy]benzoate; mp. 101.6°C (compound 8).

Example 14

A mixture of 4.1 parts of ethyl 4-(2-chloroethoxy)benzoate, 3.8 parts of intermediate 13, 3.2 parts of sodium carbonate and 47 parts of N,N-dimethylformamide was stirred overnight at 80°C. After cooling, the reaction mixture was poured into water and the product was extracted with methylbenzene. The extract was washed, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of dichloromethane and methanol (99:1 by volume) as eluent. The desired fraction was collected and the eluent was evaporated. The residue was crystallized from 2-propanol. The product was filtered off, washed and dried in vacuo at 50°C, yielding 3.1 parts (50.2%) of ethyl 4-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethoxy]benzoate; mp. 101.5°C (compound 53).

Example 15

A mixture of 4 parts of 1-chloro-4-(4-chlorobutoxy)benzene, 3.3 parts of 2-(1-piperazinyl)benzothiazole, 6.4 parts of sodium carbonate and 200 parts of 4-methyl-2-pentanone was stirred for 80 hours at reflux temperature using a water separator. After cooling, water was added and the layers were separated. The organic layer was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (99:1 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 2-propanol. The product was filtered off and dried, yielding 1.4 parts (23.2%) of 2-[4-[4-(4-chlorophenoxy)butyl]-1-piperazinyl]benzothiazole; mp. 125.1°C (compound 2).

Example 16

A mixture of 8.8 parts of intermediate 18, 3.5 parts of ethyl 4-hydroxybenzoate, 5.3 parts of potassium carbonate and 141 parts of N,N-dimethylformamide was stirred overnight at 120°C. The reaction mixture was evaporated and the residue was taken up in water and a diluted sodium hydroxide solution. The product was extracted with dichloromethane. The extract was washed with water, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel first using a mixture of trichloromethane and methanol (99:1 by volume) and then a mixture of ammonium-acetate 0.5%, methanol and acetonitrile (30:40:30 by volume) as eluents. The desired fractions were collected and the eluent was evaporated. The residue was crystallized from 2-propanol. The product was filtered off, washed with 2-propanol and 2,2'-oxybispropane and dried at 60°C, yielding 1.5 parts (17.6%) of ethyl 4-[2-[1-(5-bromo-1,3,4-thiadiazol-2-yl)-3-pyrrolidinyl]ethoxy]benzoate; mp. 116.7°C (compound 60).

Example 17

To a stirred and cooled (0°C) solution of 3.9 parts of intermediate 16 in 22 parts of acetic acid anhydride 5 were added dropwise 17 parts of trifluoromethanesulfonic acid under nitrogen atmosphere. Upon completion, stirring was continued overnight at room temperature. The reaction mixture was poured into ice water and the whole was neutralized with ammonia. The product was extracted with dichloromethane. The extract was dried (+ activated charcoal), filtered and the filtrate was evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The eluent 10 of the desired fraction was evaporated and the residue was converted into the hydrochloride salt in 2-propanol. The salt was filtered off, washed with 2-propanol and 2,2'-oxybispropane and dried at 60°C, yielding 0.8 parts (20.2%) of ethyl 4-[2-[1-(5-methyl-1,3,4-oxadiazol-2-yl)-4-piperidinyl]ethoxy]benzoate monohydrochloride; mp. 163.4°C (compound 58).

Example 18

To a stirred mixture of 2.6 parts of N-hydroxypropanimidamide and 178 parts of tetrahydrofuran were added portionwise 1.44 parts of a dispersion of sodium hydride in mineral oil (50%). After stirring for 1 hour at room temperature, there were added 5.9 parts of compound 62. The whole was refluxed overnight. The reaction mixture was evaporated and the residue was diluted with water. The precipitate was filtered off, washed with water and taken up in dichloromethane. This solution was washed with water, separated, dried, filtered and evaporated. The residue was crystallized from 2-propanol. The product was filtered off, washed with 2-propanol and dried at 50°C, yielding 3.0 parts (47.7%) of 1-(5-chloro-2-thiazolyl)-4-[2-[4-(3-ethyl-1,2,4-oxadiazol-5-yl)phenoxy]-ethyl]piperidine; mp. 101.5°C (compound 63).

25 The compounds listed in Table 1 were prepared according to similar procedures as described in any of the preceding examples 8 - 18.

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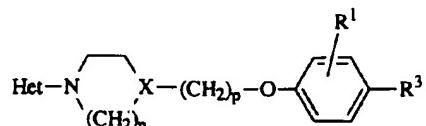
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Table 1



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Comp. No.	Ex. No.	Het	n	X	p	R ¹	R ³	mp./physical data
1	14		2	N	4	H	F	128.6°C
2	15		2	N	4	H	Cl	125.1°C
3	14		2	N	3	3-F	H	95.8°C
4	14		2	N	3	3-F	H	148.0°C / (Z) * (1:1)
5	14		2	N	4	H	F	164.2°C / (Z) * (1:1)
6	8		2	CH	2	H	COOC ₂ H ₅	91.4°C
7	13		2	CH	2	H	COOC ₂ H ₅	108.1°C
8	13		2	CH	2	H	COOC ₂ H ₅	101.6°C
9	10		2	CH	2	H	COOC ₂ H ₅	79.9°C
10	10		2	CH	2	H	COOC ₂ H ₅	79.8°C / (Z) * (1:1) / H ₂ O
11	9		2	CH	2	H	COOC ₂ H ₅	120.1°C
12	8		2	CH	2	H	COOC ₂ H ₅	101.1°C
13	8		2	CH	2	H	COOC ₂ H ₅	98.5°C

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Comp. No.	Ex. No.	Het	n	X	p	R1	R ³	mp./physical data
10	14		2	CH	2	H	COOC ₂ H ₅	189.0°C
15	15		2	CH	2	H	COOC ₂ H ₅	74.4°C
20	16		2	CH	2	H	COOC ₂ H ₅	122.2°C
25	17		2	CH	2	H	COOC ₂ H ₅	84.3°C
30	18		2	CH	2	H	COOC ₂ H ₅	144.7°C
35	19		2	CH	2	H	COOC ₂ H ₅	103.3°C
40	20		2	CH	2	H	COOC ₂ H ₅	85.8°C
45	21		2	N	3	H	COOC ₂ H ₅	116.7°C
50	22		2	N	3	2-Cl	OCH ₃	111.8°C
55	23		2	N	2	H	COOC ₂ H ₅	143.6°C
55	24		2	N	3	2-Cl	OCH ₃	137.8°C
55	25		2	N	2	H	COOC ₂ H ₅	110.1°C

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Comp. No.	Ex. No.	Het	n	X	p	R ¹	R ³	mp./physical data
26	8		2	N	3	2-Cl	OCH ₃	143.6°C
27	8		2	N	2	H	COOC ₂ H ₅	95.1°C
28	8		2	N	2	H	COOC ₂ H ₅	142.4°C
29	8		2	N	3	H	COOC ₂ H ₅	113.0°C
30	8		2	N	3	H	COOC ₂ H ₅	180.4°C
31	10		2	N	3	H	COOC ₂ H ₅	132.9°C
32	10		2	N	3	2-Cl	OCH ₃	126.5°C
33	8		2	N	2	2-Cl	OCH ₃	121.6°C
34	9		2	N	2	H	COOC ₂ H ₅	88.5°C
35	8		2	N	3	H	COOC ₂ H ₅	136.9°C
36	8		2	N	2	H	COOC ₂ H ₅	110.8°C
37	8		2	N	2	2-Cl	OCH ₃	213.1°C / 2 HCl
38	10		2	N	2	2-Cl	OCH ₃	205.6°C / HCl
39	10		2	N	2	2-Cl	OCH ₃	92.5°C
40	8		2	N	3	2-Cl	OCH ₃	112.0°C

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Comp. No.	Ex. No.	Het	n	X	p	R ¹	R ³	mp./physical data
41	10		2	N	3	H	COOC ₂ H ₅	116.5°C
42	10		2	N	3	2-Cl	OCH ₃	113.1°C
43	11		2	N	3	H	COOC ₂ H ₅	161.2°C
44	8		2	N	3	2-Cl	OCH ₃	131.8°C / (Z) * (1:2)
45	8		2	N	3	H	COOC ₂ H ₅	113.7°C
46	10		2	N	2	H	COOC ₂ H ₅	119.6°C
47	8		2	N	2	2-Cl	OCH ₃	116.0°C
48	9		2	N	2	2-Cl	OCH ₃	158.8°C / 2 HCl
49	9		2	N	3	H	COOC ₂ H ₅	168.7°C / HCl
50	14		2	N	3	2-Cl	OCH ₃	79.0°C
51	14		2	N	2	2-Cl	OCH ₃	73.8°C
52	14		2	N	3	2-Cl	OCH ₃	78.5°C
53	14		2	N	2	H	COOC ₂ H ₅	101.5°C
54	14		2	N	2	H	COOC ₂ H ₅	97.5°C

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Comp. No.	Ex. No.	Het	n	X	p	R ¹	R ³	mp./physical data
55	14		2	N	3	H	COOC ₂ H ₅	103.3°C
56	9		2	CH	2	H	COOC ₂ H ₅	123.2°C
57	9		2	N	2	H	COOC ₂ H ₅	171.4°C / (E)* (1:1)
58	17		2	CH	2	H	COOC ₂ H ₅	163.4°C / HCl
59	9		2	N	3	2-Cl	OCH ₃	185.4°C / (E)* (1:1)
60	16		1	CH	2	H	COOC ₂ H ₅	116.7°C
61	18		2	CH	2	H		125.3°C
62	10		2	CH	2	H	COOC ₂ H ₅	96.0°C
63	18		2	CH	2	H		101.5°C

* = -(2)-butenedioate

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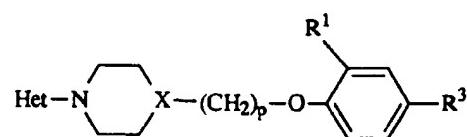
Example 19

The compounds listed in Table 2 are prepared according to similar procedures as described in any of the preceding examples 8 - 18.

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Table 3



Comp. No.	Het	X	p	R ¹	R ³
64		CH	2	H	COOC ₂ H ₅
65		CH	2	H	COOC ₂ H ₅
66		CH	2	H	COOC ₂ H ₅
67		CH	2	H	COOC ₂ H ₅
68		CH	3	H	COOC ₂ H ₅
69		CH	2	H	COOCH ₃
70		N	2	H	COOC ₂ H ₅
71		N	2	H	COOC ₂ H ₅
72		N	2	Cl	OCH ₃
73		N	2	H	COOC ₂ H ₅
74		CH	2	H	COOC ₂ H ₅
75		N	2	Cl	OCH ₃
76		N	2	Cl	OCH ₃

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C. Biological Examples

- 5 The strong antiviral activity of the compounds of formula (I) is clearly evidenced by the data obtained in the following experiment, which data are given to illustrate the useful antiviral properties of all the compounds of formula (I).

Example 20: Picornavirus Minimal Inhibitory Concentration Test.

- 10 The Minimal Inhibitory Concentration of the compounds of the present invention against the Human Rhinovirus strains (HRV) -2,-9,-14,-15,-29,-39,-41,-42,-45,-51,-59,-63,-70,-72,-85,-86 and -89 was determined by a standard cytopathic effect reduction assay as follows. To each of the ninety six (96) wells of a microtiter 96 well tissue culture plate there was added 60 µl of a Ohio Hela cell maintenance medium [Eagle's Basal medium supplemented with 5% Foetal Calf Serum (FCS)].
- 15 To two wells there was added 60 µl of an appropriate starting dilution of a compound of formula (I) and two-fold dilutions were made to cover a wide range of compound concentrations. Subsequently there were added 120 µl of an infectious solution of virus in Eagle's Basal Medium with 2% Hepes buffer, 2% FCS and 30 mM MgCl₂ to all wells except cell and compound controls. Said infectious virus solution having a TCID₅₀-value (Tissue Culture Infectious Dose) of about 100.
- 20 The TCID₅₀-value is the dose of viruses which initiates a cytopathic effect in 50% of the inoculated cells. 150 µl of the thus obtained virus-compound mixtures were then transferred to microtitre plates with subconfluent Ohio Hela Cells, grown in 100 µl of maintenance medium. Appropriate virus controls, cell controls and compound controls were included in each test. Plates were incubated for 3 to 5 days at 33°C in 5% CO₂ atmosphere. They were checked daily by light microscopy without staining and read when the virus controls showed 100% cytopathic effect (CPE) and the virus back titration confirmed that a TCID₅₀-value between 32 and 256 had been used in the test. The IC₅₀-value for each virus-compound series was taken as the concentration in ng/ml that protected 50% of the cells from cytopathic effects with respect to the untreated controls. In the standard test procedure, the compounds were tested against two panels of rhinoviruses, a first panel consisting of serotypes HRV- 2,-29,-39,-85,-9,-15,-51,-59,-63,-89,-41 and the other panel consisting of HRV-42,-45,-14,-70,-72 and -86.
- 25 The IC₅₀-value for each rhinovirus serotype was determined, and the efficacy of each compound was determined in terms of the Med₁-value and Med₂-value, which is the medium value of the IC₅₀-values of all serotypes from the first and second panel respectively.
- 30 The following table gives the testing results with the compounds of the invention.

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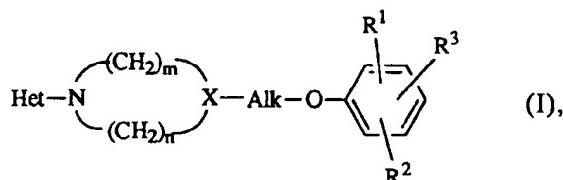
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Activity of antirhinoviral compounds		
Comp. No.	Med ₁ (ng/ml)	Med ₂ (ng/ml)
6	31	400
13	10	35
14	53	344
17	6	70.5
19	144	250
27	44	11
29	175	37
34	88	9
35	376	172
46	312	27
49	156	97
61	11	244

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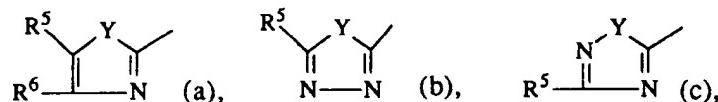
30 **Claims**

1. A compound having the formula:

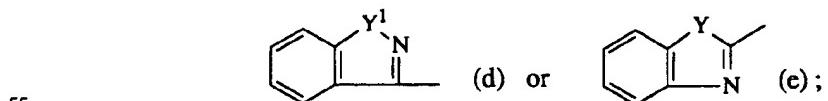


an addition salt thereof or a stereochemically isomeric form thereof, wherein
Het represents a heterocycle of formula :

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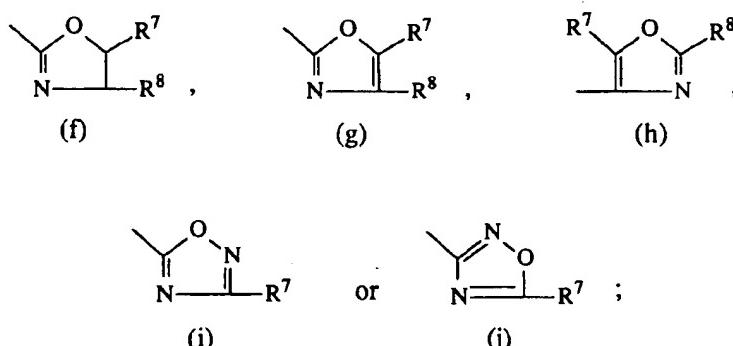


Y is O or S; Y1 is O, S or SO₂; and
R⁵ and R⁶ each independently are hydrogen, trifluoromethyl, halo, amino,
C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkyloxycarbonyl or aryl; and

m and n each independently are integers of from 1 to 4 inclusive, with the sum of m and n being 3, 4 or 5; X is N or CH:

Alk is C₁₋₄-alkanediyl:

- 5 R¹ and R² each independently are hydrogen, C₁₋₄alkyl or halo;
R³ is hydrogen, halo, cyano, C₁₋₄alkyloxy, aryl or -COOR⁴, with R⁴ being hydrogen, C₁₋₄alkyl, arylC₁₋₄alkyl, C₃₋₆cycloalkylC₁₋₄alkyl, C₃₋₆alkenyl, C₃₋₅alkynyl or C₁₋₄alkyloxyC₁₋₄alkyl; or R³ is a radical of formula



R⁷ and R⁸ each independently are hydrogen, C₁₋₄alkyl, aryl or arylC₁₋₄alkyl;

wherein each aryl is phenyl being optionally substituted with 1 or 2 substituents each independently selected from halo, C₁₋₄alkyl, trifluoromethyl, C₁₋₄alkyloxy or hydroxy, provided that Y¹ is other than S when R¹, R² and R³ represent hydrogen. X is N and m and n are both 2.

- 30 2. A compound according to claim 1 wherein n is 1, 2 or 3 and Het is a radical of formula (a) wherein R⁵ is hydrogen or halo and R⁶ is hydrogen, C₁₋₄alkyl, C₁₋₄alkyloxycarbonyl or aryl, or a radical of formula (b) wherein R⁵ is hydrogen, C₁₋₄alkyl, halo, amino or aryl, or a radical of formula (c) wherein R⁵ is hydrogen, C₁₋₄alkyl or aryl, or a radical of formula (d) or (e); or wherein R¹ and R² each independently are hydrogen or halo; R³ is a radical of formula -COOR⁴ wherein R⁴ represents C₁₋₄alkyl, C₃₋₅alkenyl, C₃₋₅alkynyl or C₁₋₄alkyloxy-C₁₋₄alkyl, or R³ is a heterocycle of formula (f), (g), (h), (i) or (j) wherein R⁷ and R⁸ each independently represent hydrogen or C₁₋₄alkyl.

35 3. A compound according to claim 2 wherein Het is a radical of formula (a) wherein R⁵ is hydrogen and R⁶ is hydrogen or C₁₋₄alkyloxycarbonyl, or a radical of formula (b) wherein R⁵ is hydrogen, C₁₋₄alkyl, halo or aryl, or a radical of formula (d) wherein Y¹ is SO₂, or a radical of formula (e); R¹ and R² are both hydrogen; R³ is C₁₋₄alkyloxycarbonyl or a 1,2,4-oxadiazol-5-yl of formula (i) wherein R⁷ represents C₁₋₄alkyl.

40 4. A compound according to claim 3 wherein n and m are both 2 and Het is a radical of formula (b) wherein R⁵ represents hydrogen, methyl, ethyl, chloro, bromo or iodo, and Y is S.

45 5. A compound according to claim 1 wherein the compound is ethyl 4-[2-[1-(5-methyl-1,3,4-thiadiazol-2-yl)-4-piperidinyl]ethoxy]benzoate, ethyl 4[2-[1-(5-bromo-1,3,4-thiadiazol-2-yl)-4piperidinyl]ethoxy]benzoate or 1-(5-bromo-1,3,4-thiadiazol-2-yl)-4-[2-[4-(3-ethyl-1,2,4-oxadiazol-5-yl)phenoxy]-ethyl]piperidine.

50 6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound as claimed in any of claims 1 to 5.

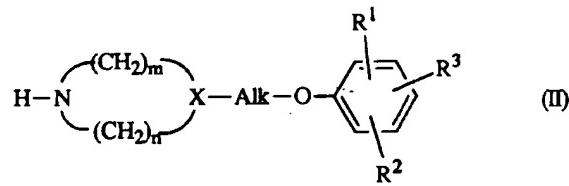
7. A composition according to claim 6 further comprising a cyclodextrin or a derivative thereof.

55 8. A method of preparing a pharmaceutical composition as claimed in claims 6 or 7, characterized in that a therapeutically effective amount of a compound as claimed in any of claims 1 to 5 is intimately mixed with a pharmaceutical carrier.

9. A compound as claimed in any of claims 1 to 5 for use as a medicine.

10. A process of preparing a compound as claimed in any of claims 1 to 5 characterized by

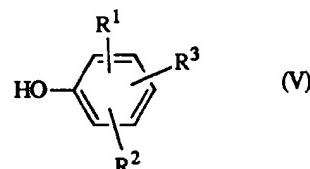
a) N-alkylating an amine of formula



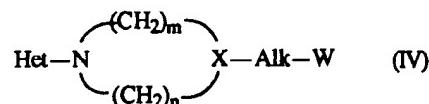
wherein R¹, R², R³, X, Alk, m and n are as defined in claim 1 with a heterocycle of formula Het-W (III)

wherein Het is as defined in claim 1 and W represents a reactive leaving group, in a reaction-inert solvent;

b) O-alkylating a phenol of formula

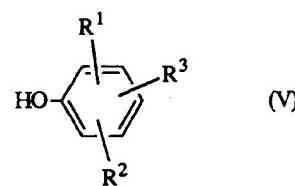


wherein R¹, R² and R³ are as defined in claim 1 with an intermediate of formula

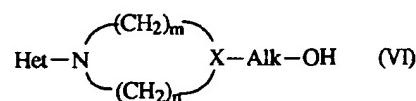


wherein Het, X, Alk, m and n are as defined in claim 1 and W represents a reactive leaving group, in a reaction-inert solvent;

c) O-alkylating a phenol of formula

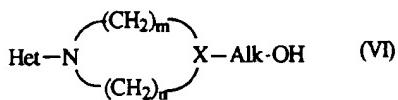


wherein R¹, R² and R³ are as defined in claim 1 with an alcohol of formula

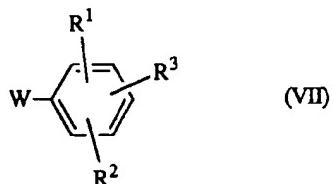


wherein Het, X, Alk, m and n are as defined in claim 1, in the presence of diethyl azodicarboxylate and triphenylphosphine in an anhydrous reaction-inert solvent;

d) O-alkylating an alcohol of formula

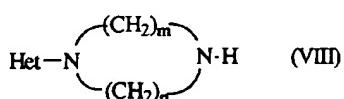


wherein Het, X, Alk, m and n are as defined in claim 1 with a reagent of formula

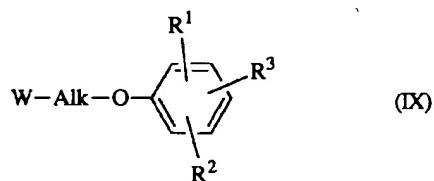


wherein R¹, R² and R³ are as defined in claim 1 and W represents a reactive leaving group, in a reaction-inert solvent;

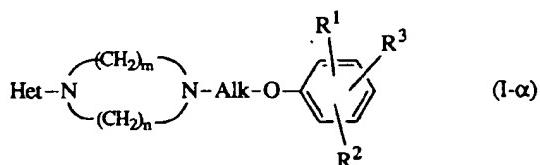
e) N-alkylating an amine of formula



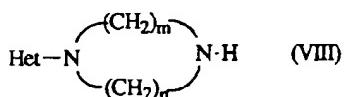
wherein Het, m and n are as defined in claim 1 with a reagent of formula



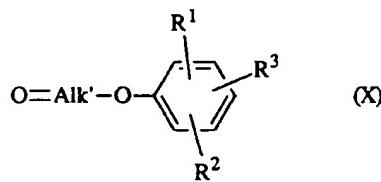
wherein R¹, R², R³ and Alk are as defined in claim 1 and W represents a reactive leaving group, in a reaction-inert solvent, thus preparing a compound of formula



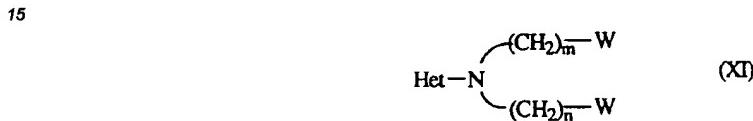
f) reductively N-alkylating an amine of formula



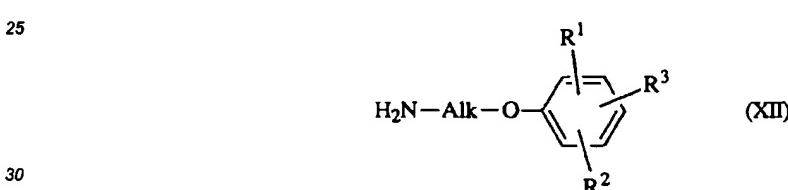
wherein Het, m and n are as defined in claim 1 with a reagent of formula



10 wherein R¹, R² and R³ are as defined in claim 1 and O=Alk' represents a radical of formula H-Alk wherein two geminal hydrogen atoms are replaced by oxygen, in a reaction-inert solvent, thus preparing a compound of formula (I- α);
g) cyclizing an intermediate of formula



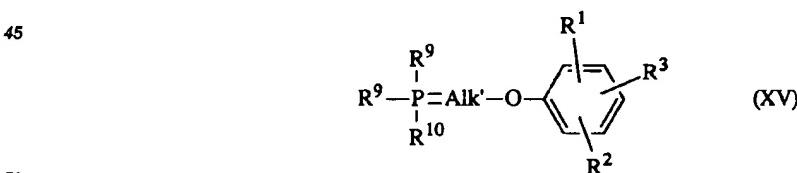
20 wherein Het, m and n are as defined in claim 1 and W represents a reactive leaving group, with an amine of formula



wherein R¹, R², R³ and Alk are as defined in claim 1, in a reaction-inert solvent, thus preparing a compound of formula (I- α);
h) reacting a ketone of formula

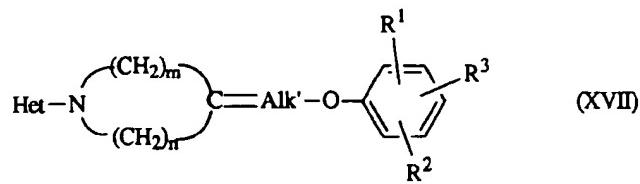


wherein Het, m and n are as defined in claim 1, with an ylide of formula



55 wherein R¹, R² and R³ are as defined in claim 1; R⁹ and R¹⁰ are aryl or C₁₋₆ alkyl, or R⁹ is alkyloxy and R¹⁰ is O⁻, and (R⁹)₂R¹⁰P=Alk' represents a radical of formula H-Alk- wherein two geminal hydrogen atoms are replaced by (R⁹)₂R¹⁰P= in a reaction-inert solvent, and subsequently reducing the thus obtained intermediate

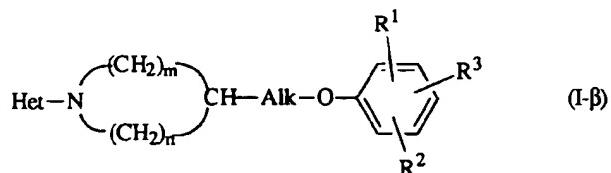
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in the presence of hydrogen and a catalyst in a reaction-inert solvent, thus yielding a compound of formula

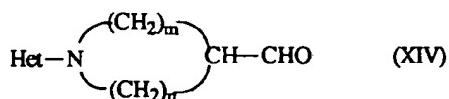
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i) reacting an aldehyde of formula

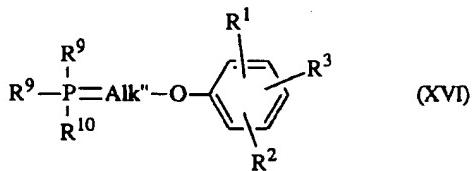
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wherein Het, m and n are as defined in claim 1 with an ylide of formula

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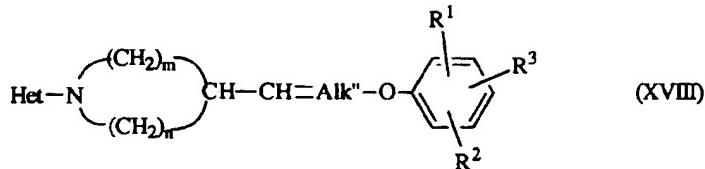


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wherein R¹, R² and R³ are as defined in claim 1; R⁹ and R¹⁰ are aryl or C₁₋₆alkyl, or R⁹ is alkoxy and R¹⁰ is O⁻, and (R⁹)₂R¹⁰P=Alk'' - represents a radical of formula H-Alk- wherein two geminal hydrogen atoms are replaced by (R⁹)₂R¹⁰P= and one methylene is lacking, in a reaction-inert solvent, and subsequently reducing the thus obtained intermediate

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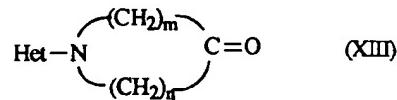
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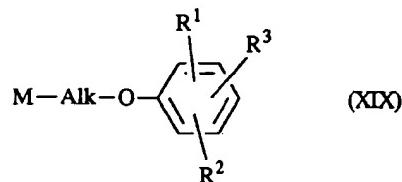
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in the presence of hydrogen and a catalyst in a reaction-inert solvent, thus yielding a compound of formula (I-β);

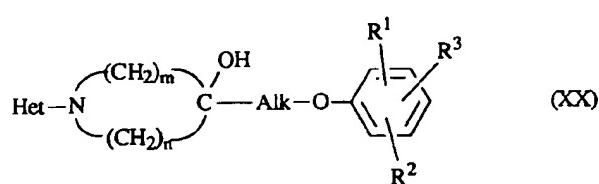
j) reacting a ketone of formula



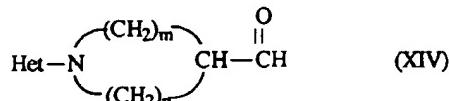
wherein Het, m and n are as defined in claim 1 with an organometallic reagent of formula



wherein Alk, R¹, R² and R³ are as defined in claim 1 and M represents a metal group in a reaction-inert solvent, and subsequently dehydrating and hydrogenating the thus obtained intermediate

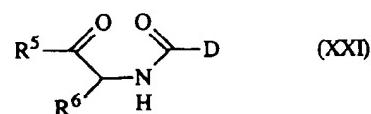


in a suitable reaction-inert solvent, thus yielding a compound of formula (I-β);
k) reacting all aldehyde of formula

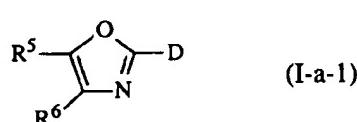


wherein Het, m and n are as defined in claim 1 with a suitable organometallic reagent, dehydrating and reducing the thus obtained intermediate in a suitable reaction-inert solvent, thus yielding a compound of formula (I-β);

l) cyclodehydrating an acylaminoketone of formula



wherein R⁵ and R⁶ are as defined in claim 1 with a dehydration reagent in a reaction-inert solvent, thus preparing a compound of formula

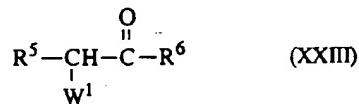


m) reacting a thiourea of formula



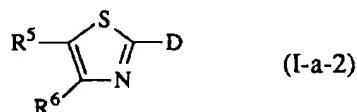
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with all α -haloketone or aldehyde of formula



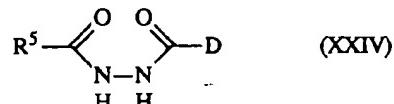
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wherein R⁵ and R⁶ are as defined in claim 1 and W¹ is halo, in a reaction-inert solvent, thus preparing a compound of formula



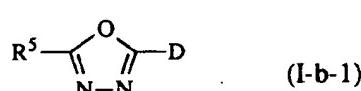
n) cyclodehydrating a diacylhydrazide of formula

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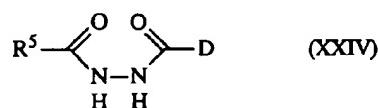
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wherein R⁵ is as defined in claim 1 with a dehydrating reagent in a reaction-inert solvent, thus preparing a compound of formula



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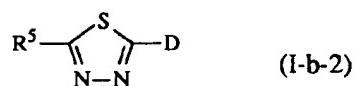
o) cyclizing a diacylhydrazide of formula



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wherein R⁵ is as defined in claim 1 with phosphorus pentasulfide in a reaction-inert solvent, thus preparing a compound of formula

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p) condensing a hydrazide of formula

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with an ortho ester of formula $\text{R}^5-\text{C}(\text{OC}_{1-4}\text{alkyl})_3$ wherein R^5 is as defined in claim 1, either in an excess of said ortho ester or in a reaction-inert solvent, thus preparing a compound of formula

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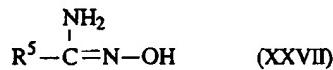
q) reacting an intermediate of formula



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wherein R^{11} is hydrogen, $\text{C}_{1-4}\text{alkyl}$ or aryl with an amidoxime of formula

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wherein R^5 is as defined in claim 1, in a reaction-inert solvent, thus preparing a compound of formula

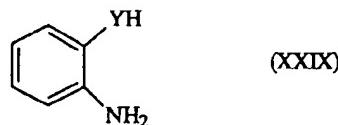
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r) reacting 2-amino(thio)phenol of formula

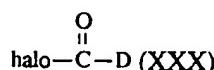
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wherein Y is O or S, with an acyl halide of formula

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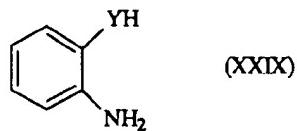


in a reaction-inert solvent, thus preparing a compound of formula

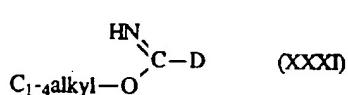
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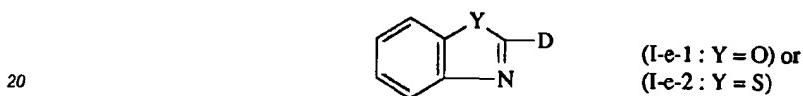
s) reacting 2-amino(thio)phenol of formula



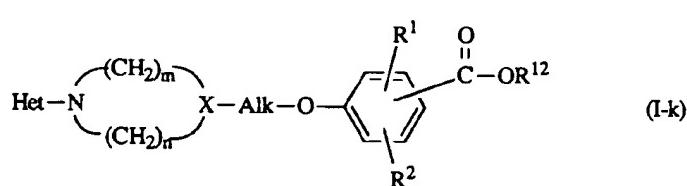
with an imidate of formula



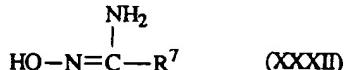
15 in a reaction-inert solvent, thus preparing a compound of formula



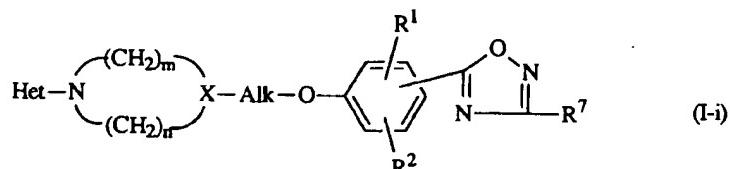
t) reacting a compound of formula



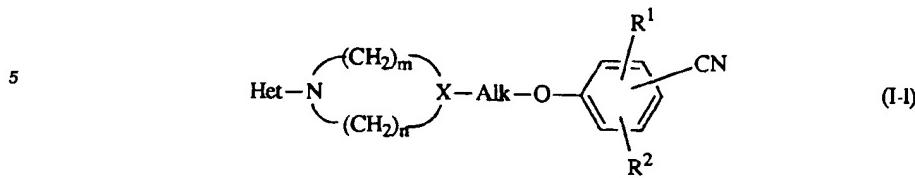
wherein Het, m, n, X, Alk, R¹ and R² are as defined in claim 1 and R¹² is hydrogen or C₁₋₄alkyl,
with an amidoimine of formula



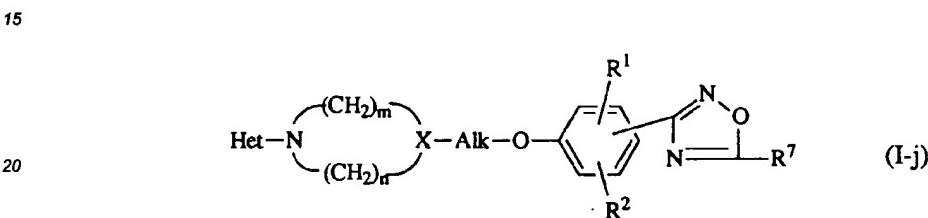
40 wherein R⁷ is as defined in claim 1 in a reaction-inert solvent thus yielding a compound of formula



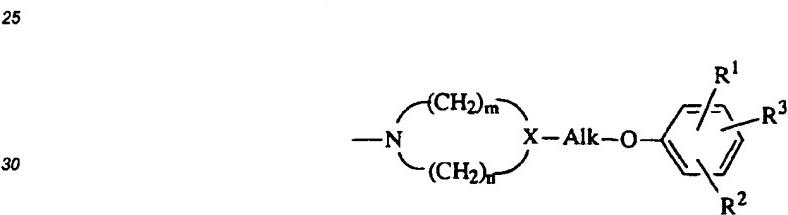
50 u) reacting a compound of formula



10 wherein Het, m, n, X, Alk, R¹ and R² are as defined in claim 1, with hydroxylamine or an acid addition salt thereof and reacting the thus formed amidoxime with a carboxylic acid of formula HOOC-R⁷ (XXXIII) wherein R⁷ is as defined in claim 1, in a reaction-inert solvent thus yielding a compound of formula



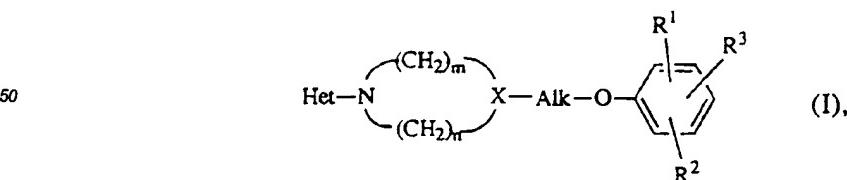
25 wherein D represents the radical



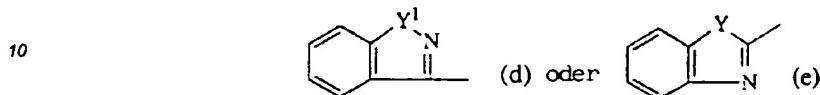
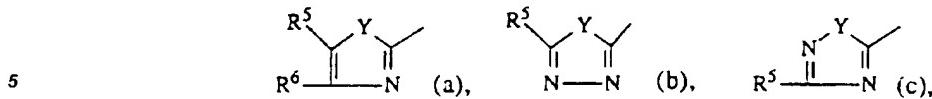
35 wherein m, n, X, Alk, R¹, R² and R³ are as defined in claim 1;
or optionally converting the compounds of formula (I) into each other following art-known functional group transformation procedures, and, if desired, converting a compound of formula (I) into a therapeutically active, acid addition salt form by treatment with an appropriate acid or, conversely, converting an acid-addition salt into a free base form with alkali; or converting a compound of formula (I) containing acidic protons into a therapeutically active non-toxic metal or amine addition salt by treatment with appropriate organic and inorganic bases; or preparing stereochemically isomeric forms thereof.

Patentansprüche

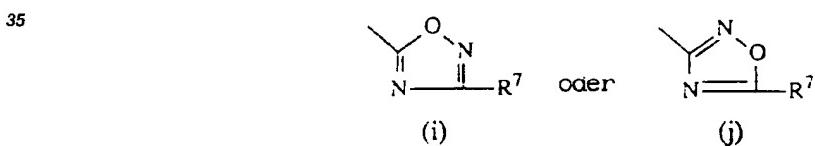
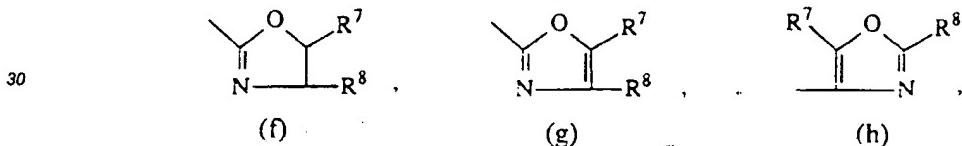
45 1. Eine Verbindung mit der Formel:



55 ein Additionssalz oder eine stereochemisch isomere Form hievon, worin
Het für einen Heterocyclus der Formel:



steht;
 15 Y die Bedeutung O oder S hat; Y¹ für O, S oder SO₂ steht; und
 R⁵ und R⁶ jeweils unabhängig voneinander Wasserstoff, Trifluormethyl, Halogen, Amino, C₁₋₄-Alkyl, C₁₋₄-Alkyloxy, C₁₋₄-Alkyloxycarbonyl oder Aryl bedeuten; und
 m und n jeweils unabhängig voneinander ganze Zahlen von 1 bis einschließlich 4 bedeuten, wobei die Summe aus m und n 3, 4 oder 5 ist;
 20 X für N oder CH steht;
 Alk die Bedeutung C₁₋₄-Alkandiyl hat;
 R¹ und R² jeweils unabhängig voneinander Wasserstoff, C₁₋₄-Alkyl oder Halogen bedeuten;
 R³ für Wasserstoff, Halogen, Cyano, C₁₋₄-Alkyloxy, Aryl oder -COOR⁴ steht, wobei R⁴ Wasserstoff, C₁₋₄-Alkyl, Aryl-C₁₋₄-alkyl, C₃₋₆-Cycloalkyl-C₁₋₄-alkyl, C₃₋₅-Alkenyl, C₃₋₅-Alkinyl oder C₁₋₄-Alkyloxy-C₁₋₄-alkyl bedeutet; oder R³ für einen Rest der Formel



40 steht;
 R⁷ und R⁸ jeweils unabhängig voneinander Wasserstoff, C₁₋₄-Alkyl, Aryl oder Aryl-C₁₋₄-alkyl bedeuten;
 wobei jedes Aryl Phenyl bedeutet, das gegebenenfalls durch 1 oder 2 Substituenten, jeweils unabhängig voneinander unter Halogen, C₁₋₄-Alkyl, Trifluormethyl, C₁₋₄-Alkyloxy oder Hydroxy ausgewählt, substituiert ist, mit der Maßgabe, daß Y¹ eine andere Bedeutung als S hat, wenn R¹, R² und R³ Wasserstoff darstellen, X die Bedeutung N hat und m und n beide 2 bedeuten.

- 45
2. Verbindung nach Anspruch 1, worin n den Wert 1, 2 oder 3 hat und Het einen Rest der Formel (a) darstellt, worin R⁵ Wasserstoff oder Halogen bedeutet und R⁸ für Wasserstoff, C₁₋₄-Alkyl, C₁₋₄-Alkyloxycarbonyl oder Aryl steht, oder einen Rest der Formel (b) bedeutet, worin R⁵ Wasserstoff, C₁₋₄-Alkyl, Halogen, Amino oder Aryl darstellt, oder einen Rest der Formel (c) bedeutet, worin R⁵ Wasserstoff, C₁₋₄-Alkyl oder Aryl darstellt, oder einen Rest der Formel (d) oder (e) bedeutet; oder worin R¹ und R² jeweils unabhängig voneinander Wasserstoff oder Halogen bedeuten; R³ für einen Rest der Formel -COOR⁴ steht, worin R⁴ C₁₋₄-Alkyl, C₃₋₅-Alkenyl, C₃₋₅-Alkinyl oder C₁₋₄-Alkyloxy-C₁₋₄-alkyl darstellt, oder R³ einen Heterocyclus der Formel (f), (g), (h), (i) oder (j) bedeutet, worin R⁷ und R⁸ jeweils unabhängig voneinander Wasserstoff oder C₁₋₄-Alkyl darstellen.
- 55
3. Verbindung nach Anspruch 2, worin Het einen Rest der Formel (a) b deutet, worin R⁵ für Wasserstoff steht

und R⁶ Wasserstoff oder C₁₋₄-Alkyloxycarbonyl darstellt, oder einen Rest der Formel (b) bedeutet, worin R⁵ für Wasserstoff, C₁₋₄-Alkyl, Halogen oder Aryl steht, oder einen Rest der Formel (d) bedeutet, worin Y¹ für SO₂ st ht, oder einen Rest der Formel (e) bedeutet; R¹ und R² beid Wasserstoff darstellen; R³ für C₁₋₄-Alkyloxycarbonyl oder in 1,2,4-Oxadiazol-5-yl der Formel (i) steht, worin R⁷ C₁₋₄-Alkyl bedeutet.

4. Verbindung nach Anspruch 3, worin n und m beide den Wert 2 aufweisen und Het einen Rest der Formel (b) bedeutet, worin R⁵ für Wasserstoff, Methyl, Ethyl, Chlor, Brom oder Iod steht und Y die Bedeutung S hat.

10 5. Verbindung nach Anspruch 1, worin die Verbindung Ethyl-4-[2-[1-(5-methyl-1,3,4-thiadiazol-2-yl)-4-piperidinyl]ethoxy]-benzoat, Ethyl-4-[2-[1-(5-brom-1,3,4-thiadiazol-2-yl)-4-piperidinyl]ethoxy]benzoat oder 1-(5-Brom-1,3,4-thiadiazol-2-yl)-4-[2-[4-(3-ethyl-1,2,4-oxadiazol-5-yl)phenoxy]ethyl]piperidin ist.

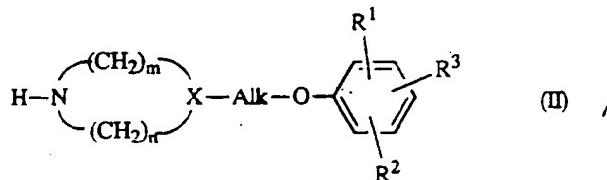
15 6. Pharmazeutische Zusammensetzung mit einem Gehalt an einem pharmazeutisch annehmbaren Träger und als wirksamem Bestandteil an einer therapeutisch wirksamen Menge einer Verbindung nach einem der Ansprüche 1 bis 5.

7. Zusammensetzung nach Anspruch 6, die zusätzlich ein Cyclodextrin oder ein Derivat hieron umfaßt.

20 8. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung nach Anspruch 6 oder 7, dadurch gekennzeichnet, daß eine therapeutisch wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 5 innig mit einem pharmazeutischen Träger vermischt wird.

25 9. Verbindung nach einem der Ansprüche 1 bis 5 zur Verwendung als ein Medikament.

10. Verfahren zur Herstellung einer Verbindung nach einem der Ansprüche 1 bis 5, gekennzeichnet durch
a) N-Alkylieren eines Amins der Formel

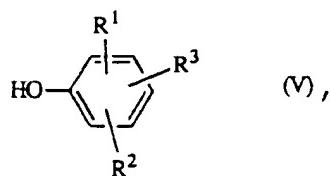


woin R¹, R², R³, X, Alk, m und n wie in Anspruch 1 definiert sind, mit einem Heterocyclus der Formel

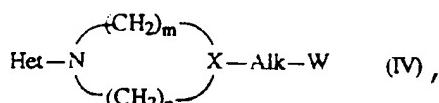
Het-W (III),

40 worin Het wie in Anspruch 1 definiert ist und W eine reaktionsfähige Leaving-Gruppe bedeutet, in einem reaktionsinternen Lösungsmittel;

b) O-Alkylieren eines Phenols der Formel



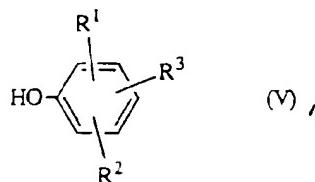
worin R^1 , R^2 und R^3 wie in Anspruch 1 definiert sind, mit einem Zwischenprodukt der Formel



worin Het, X, Alk, m und n wie in Anspruch 1 definiert sind und W eine reaktionsfähige Leaving-Gruppe bedeutet, in einem reaktionsinerten Lösungsmittel;
 c) O-Alkylieren eines Phenols der Formel

5

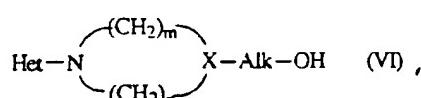
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worin R¹, R² und R³ wie in Anspruch 1 definiert sind, mit einem Alkohol der Formel

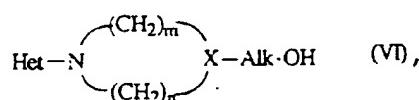


25

30

worin Het, X, Alk, m und n wie in Anspruch 1 definiert sind, in Anwesenheit von Diethylazodicarboxylat und Triphenylphosphin in einem wasserfreien reaktionsinerten Lösungsmittel;

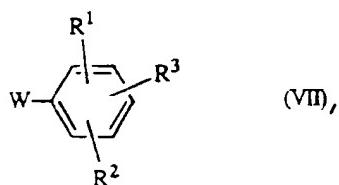
d) O-Alkylieren eines Alkohols der Formel



worin Het, X, Alk, m und n wie in Anspruch 1 definiert sind, mit einem Reagens der Formel

35

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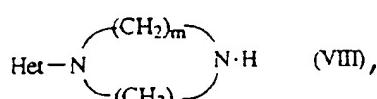


worin R¹, R² und R³ wie in Anspruch 1 definiert sind und W eine reaktionsfähige Leaving-Gruppe bedeutet, in einem reaktionsinerten Lösungsmittel;

e) N-Alkylieren eines Amins der Formel

45

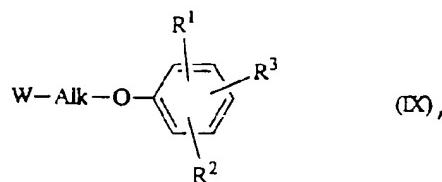
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worin Het, m und n wie in Anspruch 1 definiert sind, mit einem Reagens der Formel

55

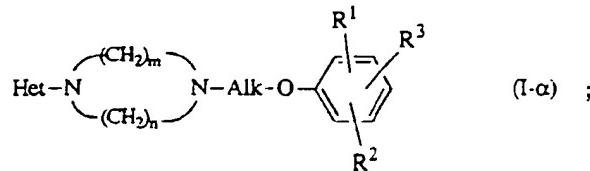
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10

worin R¹, R², R³ und Alk wie in Anspruch 1 definiert sind und W eine reaktionsfähige Leaving-Gruppe bedeutet, in einem reaktionsinerten Lösungsmittel unter Ausbildung einer Verbindung der Formel

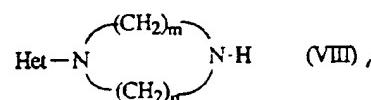
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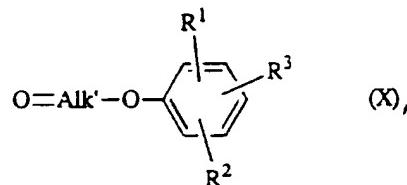
f) reduktives N-Alkylieren eines Amins der Formel

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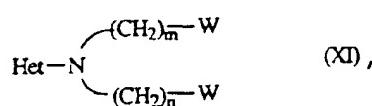


40

worin R¹, R² und R³ wie in Anspruch 1 definiert sind und O=Alk' für einen Rest der Formel H-Alk steht, worin zwei geminale Wasserstoffatome durch Sauerstoff ersetzt sind, in einem reaktionsinerten Lösungsmittel unter Ausbildung einer Verbindung der Formel (I- α);

g) Cyclisieren eines Zwischenprodukts der Formel

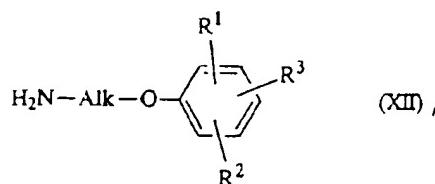
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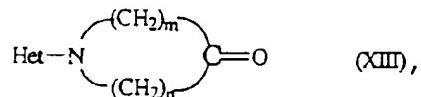
worin Het, m und n wie in Anspruch 1 definiert sind und W eine reaktionsfähige Leaving-Gruppe bedeutet, mit einem Amin der Formel

55



worin R¹, R², R³ und Alk wie in Anspruch 1 definiert sind, in einem reaktionsinerten Lösungsmittel unter Ausbildung einer Verbindung der Formel (I-α);
 h) Umsetzen eines Ketons der Formel

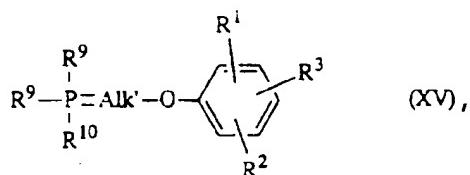
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worin Het, m und n wie in Anspruch 1 definiert sind, mit einem Ylid der Formel

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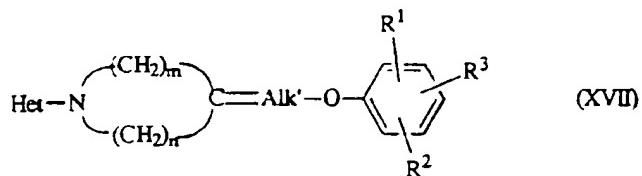


20

worin R¹, R² und R³ wie in Anspruch 1 definiert sind; R⁹ und R¹⁰ für Aryl oder C₁₋₆-Alkyl stehen, oder R⁹ Alkyloxy bedeutet und R¹⁰ für O⁻ steht, und (R⁹)₂R¹⁰P=Alk'- für einen Rest der Formel H-Alk- steht, worin zwei geminale Wasserstoffatome durch (R⁹)₂R¹⁰P= ersetzt sind, in einem reaktionsinerten Lösungsmittel und anschließendes Reduzieren des solcherart erhaltenen Zwischenproduktes

25

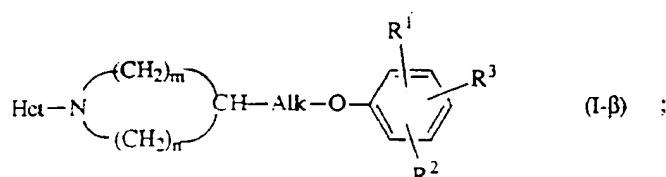
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in Gegenwart von Wasserstoff und einem Katalysator in einem reaktionsinerten Lösungsmittel unter Ausbildung einer Verbindung der Formel

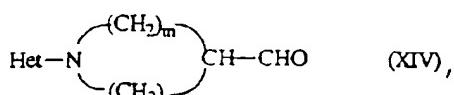
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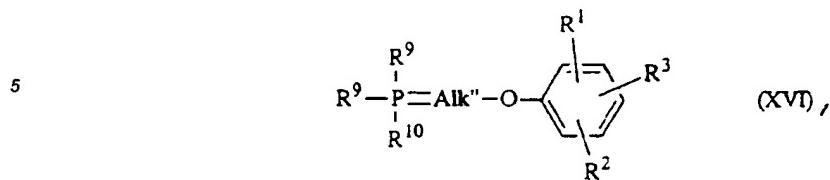
i) Umsetzen eines Aldehyds der Formel

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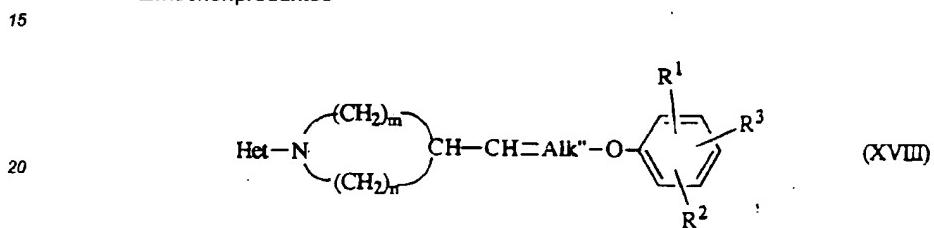


worin Het, m und n wie in Anspruch 1 definiert sind, mit einem Ylid der Formel

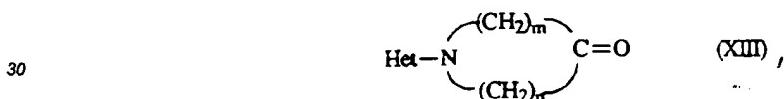
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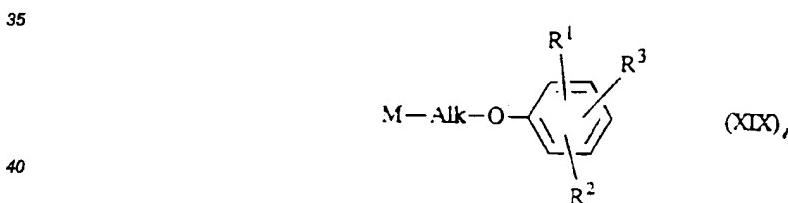
10 worin R¹, R² und R³ wie in Anspruch 1 definiert sind; R⁹ und R¹⁰ für Aryl oder C₁₋₆-Alkyl stehen, oder
R⁹ Alkyloxy darstellt und R¹⁰ für O⁻ steht, und (R⁹)₂R¹⁰P=Alk''- für einen Rest der Formel H-Alk- steht,
worin zwei geminale Wasserstoffatome durch (R⁹)₂R¹⁰P= ersetzt sind und eine Methylengruppe fehlt,
in einem reaktionsinerten Lösungsmittel und anschließendes Reduzieren des solcherart erhaltenen
Zwischenproduktes



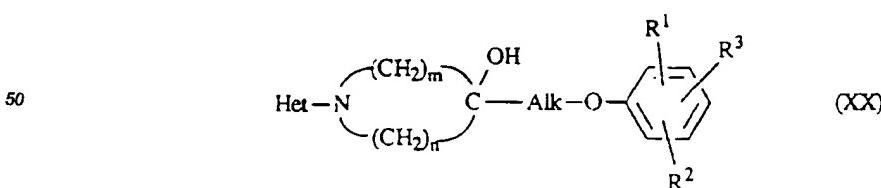
20 in Gegenwart von Wasserstoff und einem Katalysator in einem reaktionsinerten Lösungsmittel unter
Ausbildung einer Verbindung der Formel (I-β);
j) Umsetzen eines Ketons der Formel



worin Het, m und n wie in Anspruch 1 definiert sind, mit einem Organometallreagens der Formel

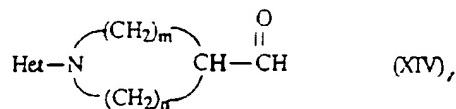


35 worin Alk, R¹, R² und R³ wie in Anspruch 1 definiert sind und M eine Metallgruppe darstellt, in einem
reaktionsinerten Lösungsmittel und anschließendes Dehydratisieren und Hydrieren des solcherart er-
haltenen Zwischenproduktes



45 in einem geeigneten reaktionsinerten Lösungsmittel unter Ausbildung einer Verbindung d r Formel (I-
β);
k) Umsetzen eines Aldehyds der Formel

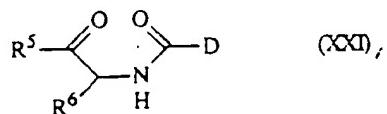
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10

worin Het, m und n wie in Anspruch 1 definiert sind, mit einem geeigneten Organometallreagens, Dehydratisieren und Reduzieren des solcherart gebildeten Zwischenproduktes in einem geeigneten reaktionsinerten Lösungsmittel unter Ausbildung einer Verbindung der Formel (I-β);
I) Cyclodehydratisieren eines Acylaminoketons der Formel

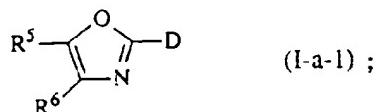
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20

worin R5 und R6 wie in Anspruch 1 definiert sind, mit einem Dehydratisierungsreagens in einem reaktionsinerten Lösungsmittel unter Ausbildung einer Verbindung der Formel

25



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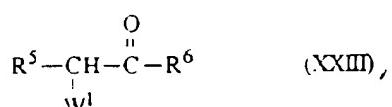
m) Umsetzen eines Thioharnstoffs der Formel



35

mit einem α-Halogenketon oder -aldehyd der Formel

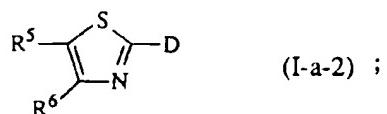
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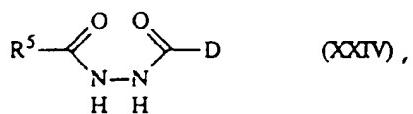
worin R5 und R6 wie in Anspruch 1 definiert sind und W1 ein Halogen darstellt, in einem reaktionsinerten Lösungsmittel unter Ausbildung einer Verbindung der Formel

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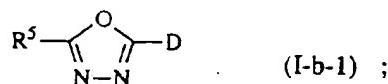
n) Cyclodehydratisieren eines Diacylhydrazids der Formel

55



worin R⁵ wie in Anspruch 1 definiert ist, mit einem Dehydratisierungsreagens in einem reaktionsinerten Lösungsmittel unter Ausbildung einer Verbindung der Formel

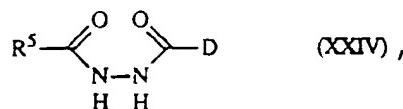
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10

o) Cyclisieren eines Diacylhydrazids der Formel

15



worin R⁵ wie in Anspruch 1 definiert ist, mit Phosphorpentasulfid in einem reaktionsinerten Lösungsmittel unter Ausbildung einer Verbindung der Formel

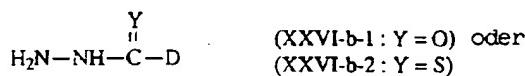
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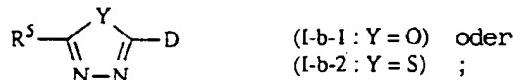
p) Kondensieren eines Hydrazids der Formel

30



mit einem Orthoester der Formel R⁵-C(OC₁₋₄-Alkyl)₃, worin R⁵ wie in Anspruch 1 definiert ist, entweder in einem Überschuß des genannten Orthoesters oder in einem reaktionsinerten Lösungsmittel unter Ausbildung einer Verbindung der Formel

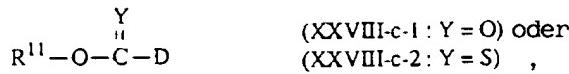
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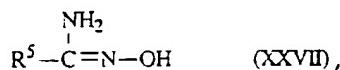
q) Umsetzen eines Zwischenprodukts der Formel

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worin R¹¹ für Wasserstoff, C₁₋₄-Alkyl oder Aryl steht, mit einem Amidoxim der Formel

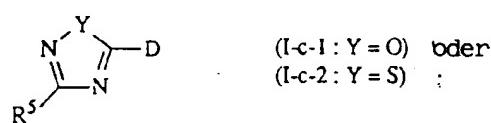
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worin R⁵ wie in Anspruch 1 definiert ist, in einem reaktionsinerten Lösungsmittel unter Ausbildung einer Verbindung der Formel

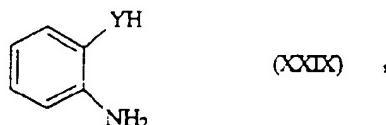
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r) Umsetzen eines 2-Amino(thio)phenols der Formel

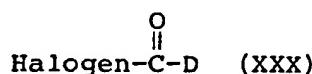
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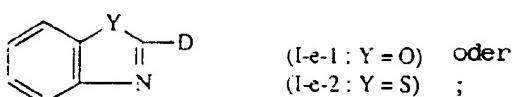
worin Y für O oder S steht, mit einem Acylhalogenid der Formel Halogen-C-D

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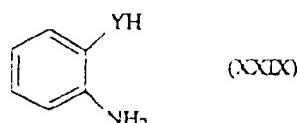
in einem reaktionsinerten Lösungsmittel unter Ausbildung einer Verbindung der Formel

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s) Umsetzen eines 2-Amino(thio)phenols der Formel

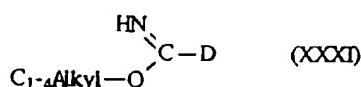
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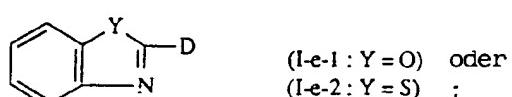
mit einem Imidat der Formel

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in einem reaktionsinerten Lösungsmittel unter Ausbildung einer Verbindung der Formel

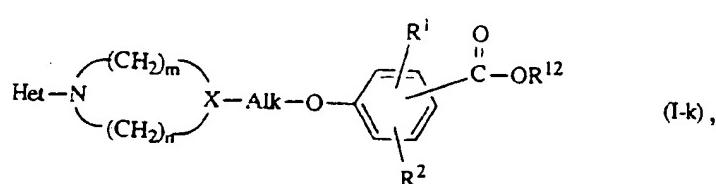
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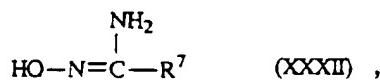
t) Umsetzen einer Verbindung der Formel

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worin Het, m, n, X, Alk, R¹ und R² wie in Anspruch 1 definiert sind und R¹² für Wasserstoff oder C₁₋₄-Alkyl steht, mit einem Amidoxim der Formel

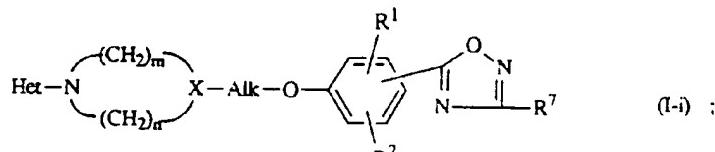
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worin R⁷ wie in Anspruch 1 definiert ist, in einem reaktionsinerten Lösungsmittel unter Ausbildung einer Verbindung der Formel

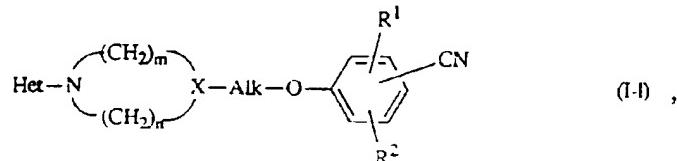
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u) Umsetzen einer Verbindung der Formel

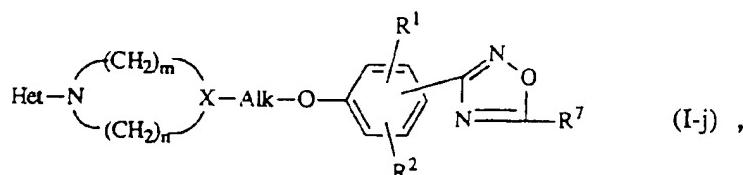
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worin Het, m, n, X, Alk, R¹ und R² wie in Anspruch 1 definiert sind, mit Hydroxylamin oder einem Säureadditionssalz hievon und Umsetzen des solcherart gebildeten Amidoxims mit einer Carbonsäure der Formel HOOC-R⁷ (XXXIII), worin R⁷ wie in Anspruch 1 definiert ist, in einem reaktionsinerten Lösungsmittel unter Ausbildung einer Verbindung der Formel

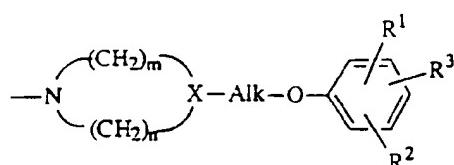
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worin D für den Rest

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steht, worin m, n, X, Alk, R¹, R² und R³ wie in Anspruch 1 definiert sind;

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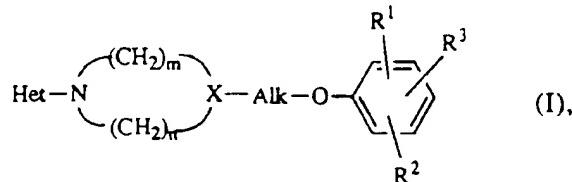
oder gewünschtenfalls Überführen der Verbindungen der Formel (I) ineinander nach literaturbekannten funktionellen Gruppentransformationsverfahren und gewünschtenfalls Umwandeln einer Verbindung der Formel (I) in eine therapeutisch wirksame Säureadditionssalzform durch Behandlung mit einer entsprechenden Säure oder umgekehrt Umwandeln eines Säureadditionssalzes in eine freie Basenform mit Alkali; oder Überführen einer Verbindung der Formel (I) mit einem Gehalt an sauren Protonen in ein therapeutisch wirksames nicht-toxisches Metall- oder Aminadditionssalz durch Behandlung mit entsprechenden organischen und anorganischen Basen; oder Herstell n stereochemisch isomerer Formen hievon.

Revendication

1. Composé ayant la formule:

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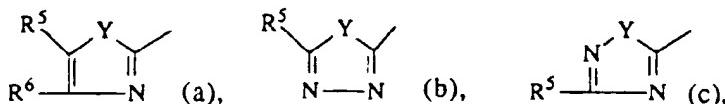


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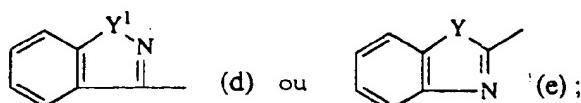
ou un sel d'addition ou une forme stéréochimiquement isomère de celui-ci, où

Het représente un hétérocycle de formule:

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Y est O ou S; Y¹ est O, S ou SO₂; et

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R⁵ et R⁶ sont, indépendamment l'un de l'autre, l'hydrogène ou un groupe trifluorométhyle, halogéno, amine, alkyle en C₁₋₄, alkyloxy en C₁₋₄, alkyloxy(C₁₋₄)carbonyle ou aryle; et m et n sont, indépendamment l'un de l'autre, des entiers de 1 à 4 inclusivement, la somme de m et n étant 3, 4 ou 5;

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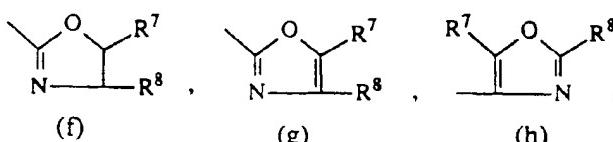
X est N ou CH;

Alk est un radical alcanediyle en C₁₋₄;R¹ et R² sont, indépendamment l'un de l'autre, l'hydrogène ou un groupe alkyle en C₁₋₄ ou halogéno;R³ est l'hydrogène ou un groupe halogéno, cyano, alkyloxy en C₁₋₄, aryle ou -COOR⁴, tandis que R⁴ est l'hydrogène ou un groupe alkyle en C₁₋₄, aryl(alkyle en C₁₋₄),

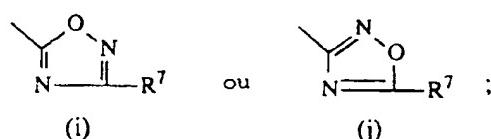
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cycloalkyl(C₃₋₆)alkyle en C₁₋₄, alcényle en C₃₋₅, alcynyle en C₃₋₅ ou (alkyloxy en C₁₋₄)alkyle en C₁₋₄; ou R³ est un radical de formule

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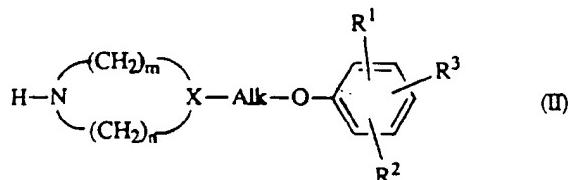


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R⁷ et R⁸ sont, indépendamment l'un de l'autre, l'hydrogène ou un groupe alkyle en C₁₋₄, aryle ou aryl(alkyle en C₁₋₄);où chaque group aryle est un radical phényle éventuellement substitué par 1 ou 2 substituants choisis indépendamment l'un de l'autre parmi les groupes halogéno, alkyl en C₁₋₄, trifluorométhyle, alkyloxy en C₁₋₄ ou hydroxy, à condition que Y¹ soit autre que S lorsque R¹, R² et R³ représentent l'hydrogène, X soit

N et m et n soient 2 tous les deux.

2. Composé selon la revendication 1, dans lequel n est 1, 2 ou 3 et Het est un radical de formule (a) où R⁵ est l'hydrogène ou un radical halogéno et R⁶ est l'hydrogène ou un groupe alkyle en C₁₋₄, alkyloxy(C₁₋₄)carbonyle ou aryle, ou un radical de formule (b) où R⁵ est l'hydrogène ou un groupe alkyle en C₁₋₄, halogéno, amino ou aryle, ou un radical de formule (c) où R⁵ est l'hydrogène ou un groupe alkyle en C₁₋₄ ou aryle, ou un radical de formule (d) ou (e); ou dans lequel R¹ et R² sont chacun, indépendamment l'un de l'autre, l'hydrogène ou un radical halogéno; R³ est un radical de formule -COOR⁴ où R⁴ représente un groupe alkyle en C₁₋₄, alcényle en C₃₋₅, alcynyle en C₃₋₅ ou alkyloxy(C₁₋₄)alkyle en C₁₋₄, ou R³ est un hétérocycle de formule (f), (g), (h), (i) ou (j) où R⁷ et R⁸ représentent chacun, indépendamment l'un de l'autre, l'hydrogène ou un groupe alkyle en C₁₋₄.
3. Composé selon la revendication 2, dans lequel Het est un radical de formule (a) où R⁵ est l'hydrogène et R⁶ est l'hydrogène ou un groupe alkyloxy(C₁₋₄)carbonyle, ou un radical de formule (b) où R⁵ est l'hydrogène ou un groupe alkyle en C₁₋₄, halogéno ou aryle, ou un radical de formule (d) où Y¹ est SO₂, ou un radical de formule (e); R¹ et R² sont tous deux de l'hydrogène; R³ est un groupe alkyloxy(C₁₋₄)carbonyle ou un groupe 1,2,4-oxadiazole-5-yle de formule (i) où R⁷ représente un groupe alkyle en C₁₋₄.
4. Composé selon la revendication 3, dans lequel n et m valent 2 tous les deux et Het est un radical de formule (b) où R⁵ représente l'hydrogène ou un groupe méthyle, éthyle, chloro, bromo ou iodo, et Y est S.
5. Composé selon la revendication 1, dans lequel le composé est le 4-[2-[1-(5-méthyl-1,3,4-thiadiazole-2-yl)-4-pipéridin-yl]éthoxylbenzoate d'éthyle, le 4-[2-[1-(5-bromo-1,3,4-thiadiazole-2-yl)-4-pipéridin-yl]éthoxylbenzoate d'éthyle, la 1-(5-bromo-1,3,4-thiadiazole-2-yl)-4-[2-[4-(3-éthyl-1,2,4-oxadiazole-5-yl)phénoxy]éthyl]pipéridine.
6. Composition pharmaceutique comprenant un support pharmaceutiquement acceptable et comme principe actif une quantité thérapeutiquement efficace d'un composé selon l'une quelconque des revendications 1 à 5.
7. Composition selon la revendication 6, comprenant en outre une cyclodextrine ou un dérivé de celle-ci.
8. Procédé pour la préparation d'une composition pharmaceutique selon l'une des revendications 6 ou 7, caractérisé en ce qu'une quantité thérapeutiquement efficace d'un composé selon l'une quelconque des revendications 1 à 5 est intimement mélangée avec un support pharmaceutique.
9. Composé selon l'une quelconque des revendications 1 à 5 pour utilisation comme médicament.
10. Procédé pour la préparation d'un composé selon l'une quelconque des revendications 1 à 5, caractérisé en ce que
 - a) on N-alkyle une amine de formule

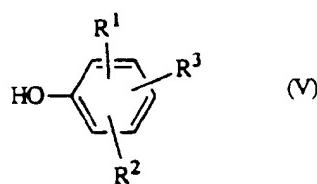


50 où R¹, R², R³, X, Alk, m et n sont tels que définis dans la revendication 1 avec un hétérocycle de formule Het-W (III)

55 où Het est tel que défini dans la revendication 1 et W représente un groupe séparable réactif, dans un solvant inerte vis-à-vis de la réaction;

b) on O-alkyle un phénol de formule

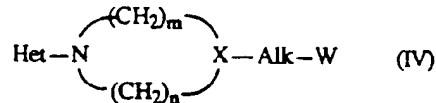
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où R¹, R² et R³ sont tels que définis dans la revendication 1 avec un intermédiaire de formule

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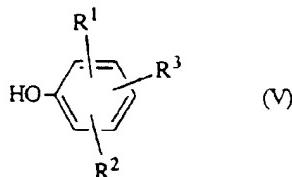


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où Het, X, Alk, m et n sont tels que définis dans la revendication 1 et W représente un groupe séparable réactif, dans un solvant inerte vis-à-vis de la réaction;

c) on O-alkyle un phénol de formule

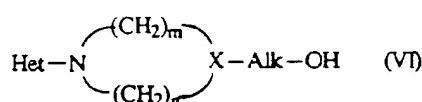
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où R¹, R²et R³ sont tels que définis dans la revendication 1 avec un alcool de formule

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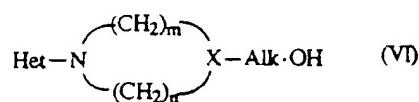


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où Het, X, Alk, m et n sont tels que définis dans la revendication 1, en présence d'azodicarboxylate de diéthyle et de triphénylphosphine dans un solvant anhydre inerte vis-à-vis de la réaction;

d) on O-alkyle un alcool de formule

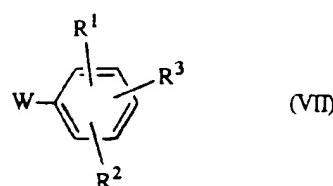
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où Het, X, Alk, m et n sont tels que définis dans la revendication 1, avec un corps réagissant de formule

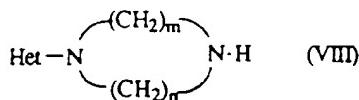
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où R¹, R² et R³ sont tels que définis dans la revendication 1 et W représente un groupe séparable réactif,

dans un solvant inert vis-à-vis de la réaction;
e) on N-alkyle une amine de formule

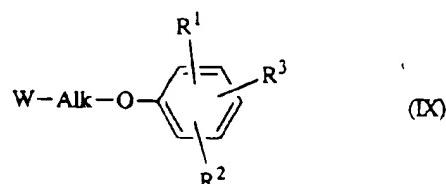
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où Het, m et n sont tels que définis dans la revendication 1, avec un corps réagissant de formule

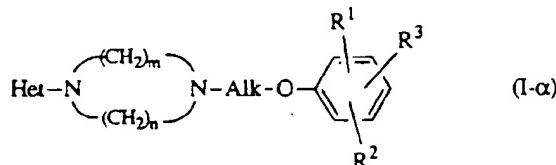
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où R¹, R², R³ et Alk sont tels que définis dans la revendication 1 et W représente un groupe séparable réactif, dans un solvant inert vis-à-vis de la réaction, préparant ainsi un composé de formule

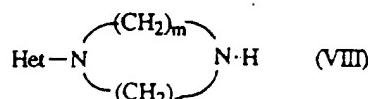
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f) on N-alkyle par réduction une amine de formule

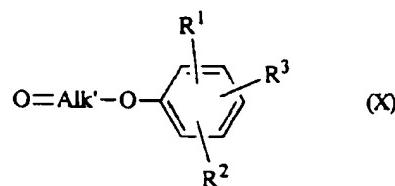
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où Het, m et n sont tels que définis dans la revendication 1, avec un corps réagissant de formule

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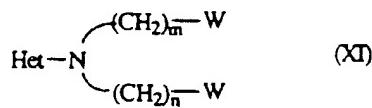


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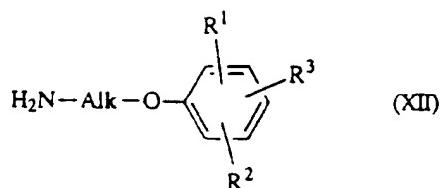
où R¹, R², R³ et Alk sont tels que définis dans la revendication 1 et O=Alk' représente un radical de formule H-Alk où deux atomes d'hydrogène géminés sont remplacés par de l'oxygène, dans un solvant inert vis-à-vis de la réaction, préparant ainsi un composé de formule (I-α);

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g) on cyclise un intermédiaire de formule

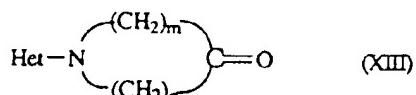


où Het, m et n sont tels que définis dans la revendication 1 et W représente un groupe séparable réactif, avec une amine de formule

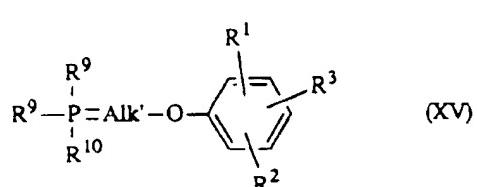


20 où R¹, R², R³ et Alk sont tels que définis dans la revendication 1, dans un solvant inert vis-à-vis de la réaction, préparant ainsi un composé de formule (I- α);

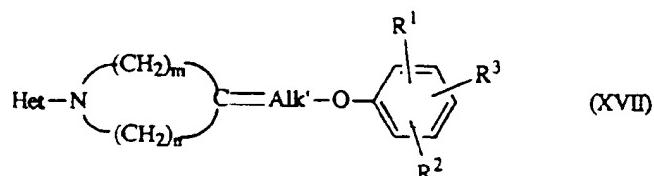
h) on fait réagir une cétone de formule



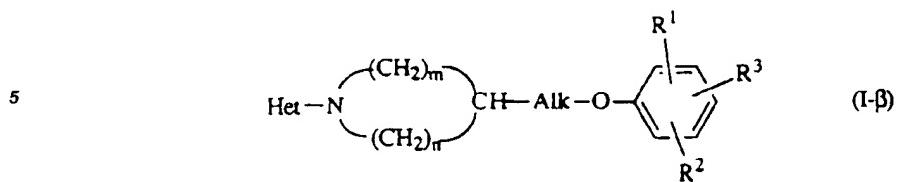
où Het, m et n sont tels que définis dans la revendication 1, avec un ylure de formule



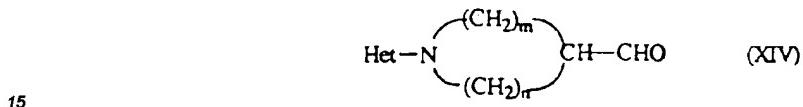
40 où R¹, R² et R³ sont tels que définis dans la revendication 1; R⁹ et R¹⁰ sont des groupes aryle ou alkyle en C₁₋₆, ou R⁹ est un radical alkoxy et R¹⁰ est O⁻, et (R⁹)₂R¹⁰P=Alk'- représente un radical de formule H-Alk- où deux atomes d'hydrogène géminés sont remplacés par (R⁹)₂R¹⁰P=, dans un solvant inert vis-à-vis de la réaction, et subséquemment on réduit l'intermédiaire ainsi obtenu



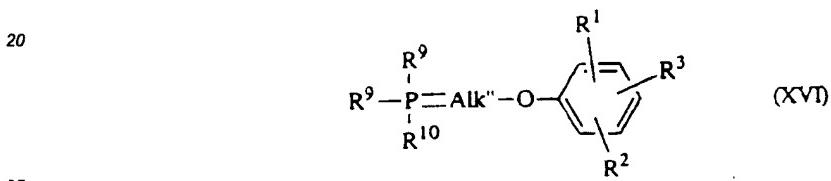
50 en présence d'hydrogène et d'un catalyseur, dans un solvant inert vis-à-vis de la réaction, formant ainsi un composé de formule



10 i) on fait réagir un aldéhyde de formule

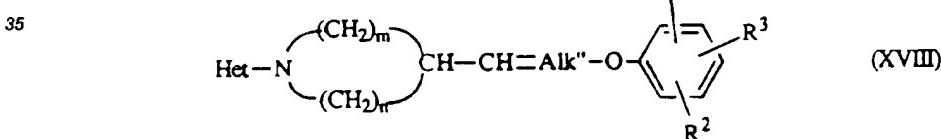


où Het, m et n sont tels que définis dans la revendication 1, avec un ylure de formule



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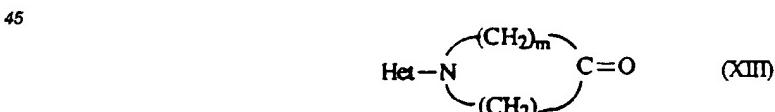
où R¹, R² et R³ sont tels que définis dans la revendication 1; R⁹ et R¹⁰ sont des groupes aryle ou alkyle en C₁₋₆; ou R⁹ est un radical alkoxy et R¹⁰ est O⁻; et (R⁹)₂R¹⁰P=Alk''- représente un radical de formule H-Alk- où deux atomes d'hydrogène géminés sont remplacés par (R⁹)₂R¹⁰P=, et un radical méthylène est manquant, dans un solvant inert vis-à-vis de la réaction, et subséquemment on réduit l'intermédiaire ainsi obtenu



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en présence d'hydrogène et d'un catalyseur, dans un solvant inert vis-à-vis de la réaction, formant ainsi un composé de formule (I-β);

j) on réduit une cétone de formule

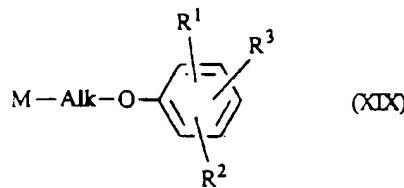


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où Het, m et n sont tels que définis dans la revendication 1, avec un corps réagissant organométallique de formule

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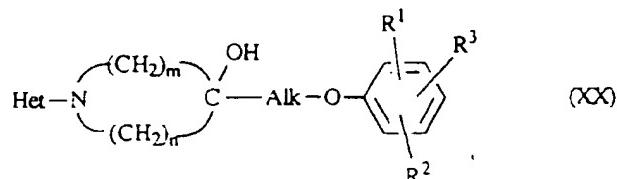
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où Alk, R¹, R² et R³ sont tels que définis dans la revendication 1 et M représente un groupe métal, dans un solvant inert vis-à-vis de 1 aréaction, et subséquemment on déhydrate et hydrogène l'intermédiaire ainsi obtenu

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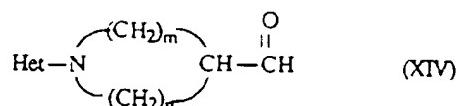


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dans un solvant inert vis-à-vis de la réaction, formant ainsi un composé de formule (I-β);
k) on fait réagir un aldéhyde de formule

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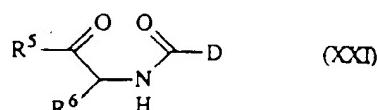


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où Het, m et n sont tels que définis dans la revendication 1, avec un corps réagissant organométallique, on déhydrate et on réduit l'intermédiaire ainsi obtenu, dans un solvant inert vis-à-vis de la réaction, formant ainsi un composé de formule (I-β);

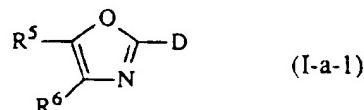
l) on cyclodéhydrate une acylaminocétone de formule

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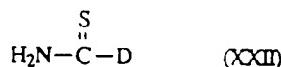
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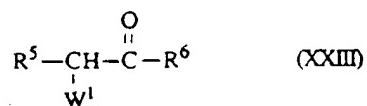


m) on fait réagir une thiourée de formule

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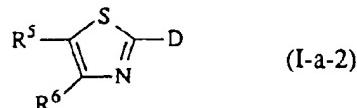


av c une α-halogénocétone de formule



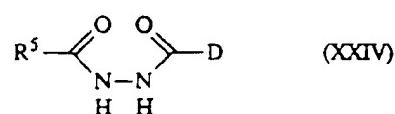
où R^5 et R^6 sont tels que définis dans la revendication 1 et W^1 est un radical halogéno, dans un solvant inerte vis-à-vis de la réaction, préparant ainsi un composé de formule

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n) on cyclodéhydrate un diacylhydrazide de formule

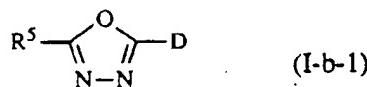
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où R^5 est tel que défini dans la revendication 1, avec un agent de déshydratation dans un solvant inerte vis-à-vis de la réaction, préparant ainsi un composé de formule

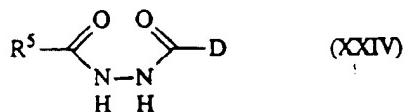
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o) on cyclise un diacylhydrazide de formule

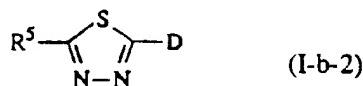
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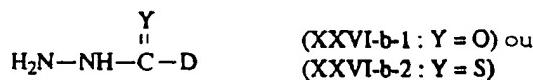
où R^5 est tel que défini dans la revendication 1, avec du pentasulfure phosphoreux, dans un solvant inerte vis-à-vis de la réaction, préparant ainsi un composé de formule

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p) on condense un hydrazide de formule

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av c un ortho est r de formule $R^5-C(Oalkyl\ en\ C_{1-4})_3$ où R^5 est tel que défini dans la revendication 1, soit en un excès du dit ortho ester, soit dans un solvant inerte vis-à-vis de la réaction, préparant ainsi un composé de formule

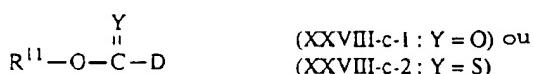
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q) on fait réagir un intermédiaire de formule

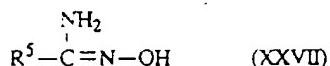
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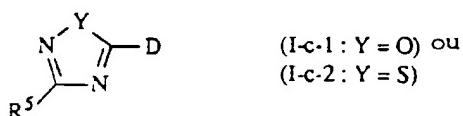
où R^{11} , est l'hydrogène ou un groupe alkyle en C_{1-4} ou aryle avec une amidoxime de formule

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où R^5 est tel que défini dans la revendication 1, dans un solvant inerte vis-à-vis de la réaction, préparant ainsi un composé de formule

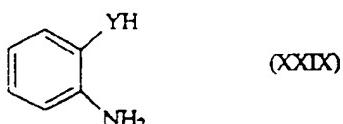
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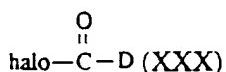
r) on fait réagir du 2-amino(thio)phénol de formule

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où Y est O ou S , avec un halogénure d'acyle de formule

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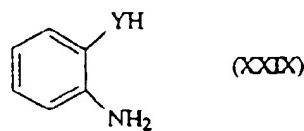
dans un solvant inerte vis-à-vis de 1 aréaction, préparant ainsi un composé de formule

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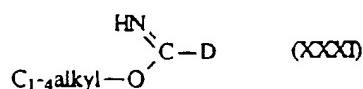
s) on fait réagir du 2-amino(thio)phénol de formule

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avec un imidate de formule

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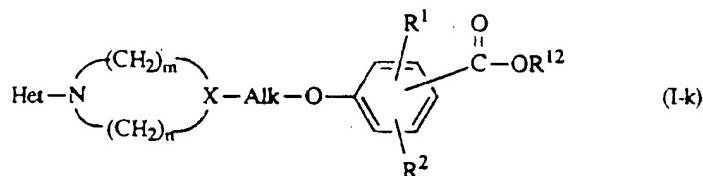
dans un solvant inerte vis-à-vis de la réaction, préparant ainsi un composé de formule

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t) on fait réagir un composé de formule

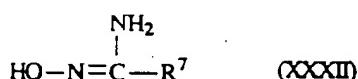
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où Het, m, n, X, Alk, R¹ et R² sont tels que définis dans la revendication 1 et R¹² est l'hydrogène ou un radical alkyle en C₁₋₄, avec une amidoxime de formule

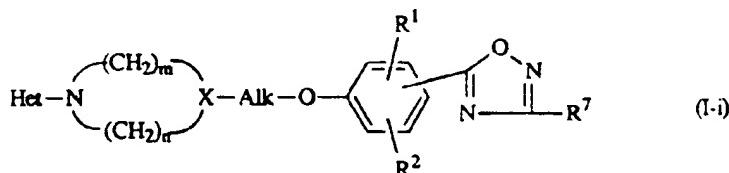
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où R⁷ est tel que défini dans la revendication 1, dans un solvant inerte vis-à-vis de la réaction, formant ainsi un composé de formule

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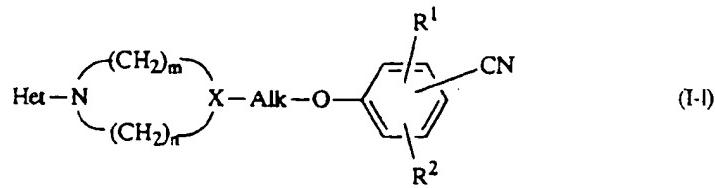


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u) on fait réagir un composé de formule

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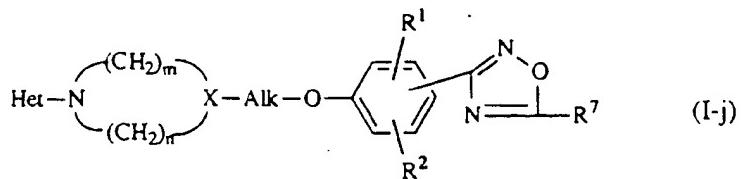


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où Het, m, n, X, Alk, R¹ et R² sont tels que définis dans la revendication 1, avec de l'hydroxylamine ou un sel d'addition d'acide de celle-ci et on fait réagir l'amidoxime ainsi formée avec un acide carboxylique de formule HOOC-R⁷ (XXXIII), où R⁷ est tel que défini dans la revendication 1, dans un solvant inerte vis-à-vis de la réaction, formant ainsi un composé de formule

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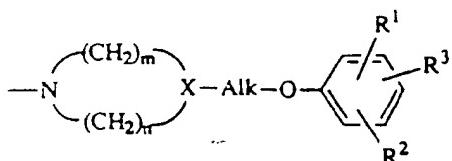
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où D représente le radical

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où m, n, X, Alk, R¹, R² et R³ sont tels que définis dans la revendication 1;
ou en option on convertit les composés de formule (I) respectivement l'un en l'autre suivant des techniques de transformation de groupe fonctionnel connues de l'homme du métier, et, si on le souhaite, on convertit un composé de formule (I) en une forme sel d'addition d'acide thérapeutiquement actif par traitement avec un acide approprié ou, au contraire, on convertit une forme sel d'addition d'acide en une forme base libre avec un alcali; ou on convertit un composé de formule (I) contenant des protons acides en un sel d'addition de métal non-toxique ou d'amine, thérapeutiquement actif, par traitement avec des bases organiques ou inorganiques appropriées; ou on prépare des formes stéréochimiquement isomères de ceux-ci.

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